Olle Ljungqvist
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Editors

Enhanced Recovery After Surgery (ERAS®)

A Complete Guide to Optimizing Outcomes

ERAS® Society

Springer

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Foreword

Since "enhanced postoperative recovery programs" (ERPs) were first described in colonic surgery in 1995, the implications of ERPs have been extensive, not only by enhancing recovery but also by reducing hospital stay and medical complications with obvious secondary significant economic benefits. In this context, the ERAS® Society has made huge contributions for worldwide assistance to spread the message of these universal surgical care programs. Furthermore, the ERP results have led to the establishment of several regional or national ERAS-type societies with several guidelines worldwide.

However, the present book is so far the most extensive document covering all aspects of ERPs, from basic pathophysiology of postoperative recovery to a detailed description of pre-, intra-, and postoperative factors to be considered for implementation. Although several chapters consider the classical well-established components such as preoperative risk assessment, avoidance of intraoperative hypothermia, etc., other chapters are new or updated such as anemia and blood management, prehabilitation, and focus on ERAS after discharge, which represents one of the major future challenges in ERAS. Importantly, the last part of the book focuses on the procedure-specific ERPs as well as administrative aspects to be considered for a more global implementation of ERAS. Finally, the book contains important information about the role of nursing care where the future in our modern busy healthcare system has to place more responsibility on nursing care to achieve the collaborative benefits of the physician-provided preoperative, intraoperative, and early postoperative management.

In summary, this so far most extensive document to help clinicians to be updated in the pathophysiological background for ERAS and to improve the implementation process fulfils a great need to spread the ERAS message. However, although being an updated documentation of ERAS, we should not forget that many future challenges lie ahead for further improvement of ERAS programs, being a dynamic process for surgical outcome improvement based on a better understanding of perioperative pathophysiology, pain management, and surgical techniques, with minimally invasive surgical approaches as well as organizational aspects of all-over care hopefully finally leading to the ultimate goal of a "pain- and risk-free operation."

Copenhagen, Denmark — Henrik Kehlet, MD, PhD

Preface

Enhanced Recovery After Surgery (ERAS) is spreading like a wildfire across the world arena of virtually all surgical disciplines and anesthesia for good reason. It results in winners at every stakeholder level: first and foremost—the patients—who suffer fewer complications, experience faster recovery, and return to normal functions and everyday life activities quicker and better. Medical staff and healthcare providers experience the satisfaction of being part of care processes where their patients are feeling and doing much better faster and their outcomes are improving. Managers see their units deliver better care for substantially less cost, and the general public ultimately experiences better care at a lower cost.

A wide range of professions and disciplines are engaged in the processes involved in the care of the surgical patient, and because ERAS is based on the entire journey of the patient, it goes without saying that every player and stakeholder plays an import part contributing to the outcomes. For this reason, the ERAS® Society has built training programs for the implementation of ERAS where teams representing all healthcare providers involved are engaged. This book was created to have everyone take advantage of a comprehensive ERAS text, as well as for all those who soon will be involved in implementing ERAS in their own units. This excellent book can also serve as a reference for students of different medical professions as well as nurses and physician assistants at different stages of their education, and we hope it will be of use in specialty practices as it describes the modern way to care for the surgical patient.

The book is built around nine sections: the first part describes the principles of enhanced recovery, and then the following three parts cover pre-, intra-, and postoperative care elements of ERAS presented in separate chapters. There is also a section on prevention of complications, a section on ERAS after discharge, and a section on safety and quality improvement in ERAS. Section 8 is a large section covering a wide range of specialties in which ERAS has been successfully employed. In the final section, several administrative aspects of ERAS are discussed including cost savings, as well as an updated review of ERAS progress in different parts of the world.

This book has been written on behalf of the ERAS® Society (www.erassociety.org), a not-for-profit organization founded in 2010. Since that time, the ERAS® Society has published a range of specialty guidelines and consensus papers for various surgical disciplines. The editors and section editors have been fortunate to have many of the authors of these guidelines, as well as a range of world experts who are driving the development and improvements in the fields of surgery, anesthesia, nursing, nutrition, physiotherapy, and perioperative medicine. We thank each and every one for their excellent contributions.

This book is dedicated to the memory of Professor Kenneth Fearon, who practiced at the University of Edinburgh, Scotland, and who was one of the founding fathers of the ERAS concept and the ERAS® Society. Ken sadly left us in 2016, but he already had the idea of the Society producing a textbook on the topic years ago, and it is our pleasure to be able to fulfill his wish.

We hope you find this book a useful source of information in your clinical practice.

Örebro, Sweden — Olle Ljungqvist, MD, PhD
Yeovil, Somerset, UK — Nader K. Francis, MBChB, FRCS, PhD
Boston, MA, USA — Richard D. Urman, MD, MBA, FASA

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We are also grateful for the significant contribution and leadership of all section editors including Francesco Carli, Hans D. de Boer, William Fawcett, Martin Hübner, Dileep Lobo, Gregg Nelson, Arthur Revhaug, Colin Royse, and Michael Scott.

A special thanks to Henrik Kehlet for his encouragement and support and for contributing the Foreword for this book.

We would like to thank Springer Publishing for having faith in this undertaking and for their continual support across all phases of production of this book – and in particular we would like to thank Gregory Sutorius, Maureen Pierce, Jeffrey Taub, Rekha Udaiyar and ArulRonika Pathinathan.

Finally, we would like to dedicate this book to the memory of our friend and colleague Ken Fearon who passed away on September 3, 2016. Professor Fearon inspired and influenced perioperative clinical practice across the world, and his contribution to, and belief in, ERAS has inspired much of what is best in this book. It is gratifying that we have been able to honor him with producing such a comprehensive textbook that covers all aspects of ERAS which he would have wanted in order to help patients and all the multidisciplinary members of the perioperative care team.

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Part I

Introduction

Enhanced Recovery After Surgery: A Paradigm Shift in Perioperative Care

1

Olle Ljungqvist

Introduction

Surgery involves a deliberate injury to the body. It is most often performed with the aim to remove a disease such as a cancer or inflammatory process (Crohn's) or to repair tissue that has become broken or damaged (hernia repair) or surgery following an accident. Surgery is one of the most utilized treatments worldwide, with an estimated 300 million major operations performed yearly [1]. Surgery can in some cases be regarded as a dangerous treatment—25% of all patients undergoing surgery will have a complication, and a significant number will die as a result.

Over the years, surgery has become increasingly complex with incorporation of highly developed techniques involving computing and advanced visualization support, which has resulted in improvements in surgical precision. Today, high-resolution screens used to enlarge and improve vision at the site of the operation are available and are commonly used for most operations that only a few decades ago were done under direct vision or at best magnifying glasses. Minimally invasive techniques and robotics have made precision surgery a daily practice in many hospitals around the world. In parallel, anesthesia has developed with advanced detailed monitoring devices controlling all vital signs, allowing for better control of pain, depth of anesthesia, relaxation, control of vital organ function, and fluid balance. New drugs allow for return to lucidity almost instantly after anesthesia, and better pain management without side effects supports very rapid return to mobilization and function. These medical and technical advances have allowed for a dramatic change in status of the surgical patient in the postoperative period, allowing for better recovery. This, alongside therapeutic improvements for cancer patients and medicine in general, has allowed for fewer complications after surgery and better overall survival in both the short and long term.

With the development of improved techniques and practice in the operating room, the needs of the postoperative patient have changed, and this has impacted nursing. At the same time, nursing has developed into a science that is evolving and complementing the more classical medical sciences in surgery and anesthesia. Nurses take on new roles and missions and advance many of the elements in the care of the patients. The same is true for nutrition care, where dietitians are becoming more and more involved in the care of the surgical patient. The realization that the stress responses activated by injury and surgery (e.g., the metabolic response) play a key role for the development of complications and delaying recovery after surgery has highlighted the need for management of such responses in the surgical patient [2]. Nutrition plays a key part in this process. While it was not long ago that patients were ordered nil per os (NPO) and strict bed rest for days after surgery, today the roles of nutrition and physical activity have come into focus. With the concept of pre-habilitation, the combination of physical training, protein-supplemented nutrition, and mental preparation has shown to impact preoperative physical capacity in a way that facilitates recovery after surgery. With this concept, the important role of the physiotherapist has been raised.

Modern technology and development of society have also influenced surgery in a different way. The growing availability of information and exchange of information has helped build the knowledge of surgery and anesthesia practice and availability around the globe. This has increased the pressure for more high-quality surgery in most countries around the world. While at different levels in different countries and regions, the pressure on surgery and healthcare in general is growing. There is a huge unmet need for surgery globally, but this is very unevenly distributed. In all societies the cost of healthcare is rising, in part because of an increasingly older population, but also because of new inventions, medications, and improvements that allow better care and

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increased chance for cure. Many of these changes, however, come with a higher cost. Thus, there is a continuous struggle to deliver more and better care, but at a lower price (or at least not a higher price).

Despite the short summaries described above of some of the more prominent developments in recent years in the care of the surgical patient, overall there is still a very slow movement toward the use of new proven methods that are better than many old traditions still in use. In a world where communication has become very cheap, modern Web-based information is spread at an unprecedented speed, and where many professions change very rapidly, surgery and anesthesia and perhaps medicine in general are slow to adopt new treatments and ways to address the care of the surgical patient. The same doctors, nurses, and allied healthcare staff who change the operating systems on their phones within minutes or, if slow, in days will not change their practice in surgery for 15 or more years. Fast-track surgery was first published as a concept in 1994 by Engelman and colleagues [3], and shortly thereafter remarkable results in recovery time were published by Kehlet and colleagues in 1995 and 1999 [4, 5]. The Enhanced Recovery After Surgery (ERAS) project was initiated in the year 2000 [6], and since then there has been an exponential development in this field with more than 600 publications registered in PubMed in 2018 alone for ERAS (Fig. 1.1). So, the knowledge has been around for a long time, yet the use of these principles is far from daily practice around the world. ERAS practice is still limited to key opinion leaders and early adopters. This becomes evident when data on length of stay from different countries are reviewed. These national data usually reveal average postoperative stays that are longer compared to what is reported when employing ERAS principles—often by 2–3 days or more. While a good ERAS program for colorectal surgery will result in recovery times that allow the patient to be perfectly fit to leave the hospital in 2–4 days, national averages for the same operations are often 6–10 days (in extreme cases 12–14 days). So, the million-dollar question is: Why is this so? There are several explanations for this, and in the following, the main ones will be highlighted.

Effect of Specialization

Performing good surgery, as always, remains a team-based activity between surgery and anesthesia in the operating room. As specialization is growing in surgery and anesthesia, there is a risk that they grow further and further apart. As specialties become more advanced, the harder it is for one to get the insights of the other. Yet, when improvements are made, they cannot work in isolation but must fit the overall care pathway; this creates an even greater need to work more closely together to make sure the improvements harmonize. This is obvious when reading most of the research published in the two specialties. A paper in anesthesia will describe the anesthesia in minute details and report on outcomes after the patient "was operated on." Many surgical papers will give the details of the operations while the patient "had anesthesia" and report on the same outcomes. None of them knows or feels the other may impact the outcomes and fails to take the other into account. Since both surgery (which operation, the technique, blood loss, etc.) and anesthesia (which type and depth of fluid management, temperature control, etc.) all have direct impact on the same recovery measures and outcomes that both are looking for, there is need for communication and continuous collaboration to develop both fields effectively. This is true for research but even more so for daily practice. To improve this situation, the ERAS® Society has published guidelines for publications on ERAS [7]. This is how ERAS and the new ways of working play its vital role.

Resources for Care

A second limiting factor lies with the available resources in parts of the world. The Lancet Commission on Global Surgery reported that there is a lack of availability of surgery

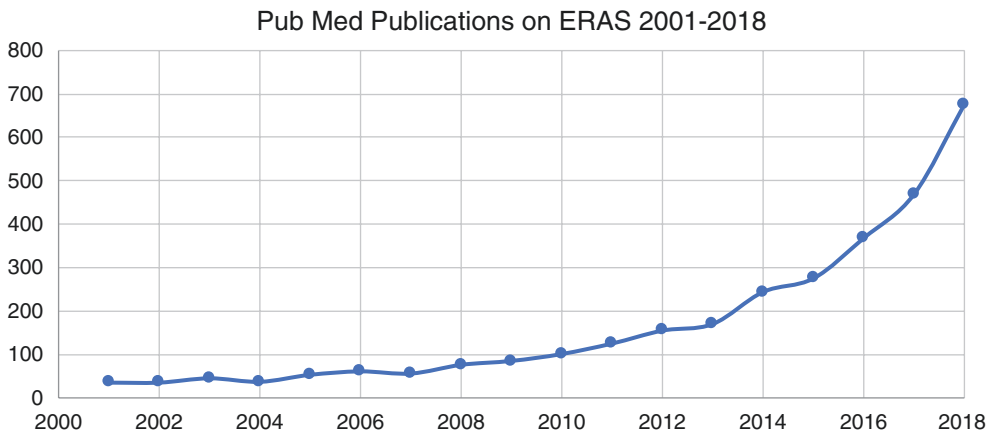

Fig. 1.1 Development of PubMed registered publications on Enhanced Recovery After Surgery

in vast parts of the world. The variation in access to care is enormous, not only between different countries [8] but in many cases also within countries [9]. There is a lack of knowledge about surgery since even the most basic data is not available in most countries [10]. Only a relatively small minority of countries can deliver accurate data on mortality after surgery. Despite these shortcomings, much of the ERAS principles can be applied in every unit regardless of resources. Communication, teamwork around practice, harmonization of care pathways, and some basic audit can be achieved everywhere.

The Role of Individual Doctors

The influence of the individual doctor on care is also a major factor. Reports on how anesthesiologists manage key aspects of care during anesthesia, such as fluids, reveal huge variations. While some may order 2 ml/kg/h for an uncomplicated abdominal procedure, others will give up to 40 ml/kg/h [11]. Since keeping fluid balance is key for outcomes, this alone shows how just one decision can impact the entire outcome [12, 13]. For surgeons, reports on outcomes also show huge variations, but these data are harder to interpret since the outcome may also be influenced by the entire care delivered in different units and different doctors in that unit—not just the operating surgeon alone. In addition, it is very hard for any one doctor to keep track of all the aspects of care by following the literature and the novel developments within their field. Most clinicians are busy managing their daily practice with little time to read literature. Many developments are driven by industry, and many of the technical advances tend to catch much of the attention. Softer changes or improvements have less chance of reaching larger audiences. This is where expert guidelines and consensus statements can play an important role in helping busy clinicians by reviewing and assembling updated knowledge from the literature.

The Basics of ERAS®

ERAS® is a new way of working. There are a few cornerstones in ERAS® (Table 1.1). The care plan is standardized and covers the entire patient journey from the first meeting with the surgeon to the follow-up visit a month after surgery.

Table 1.1 The cornerstones of ERAS®

Evidence-based perioperative care
Multidisciplinary and multi-professional approach
Teamwork
Continuous interactive audit and reporting
Data-driven change
Readiness to make the next change

Every care element in the care protocol is evidence based. The evidence base is presented in guidelines developed and reviewed by experts in the field. There is a local ERAS team formed involving all disciplines and professions involved in the patient's care. This team develops and institutes the ERAS principles at the home unit based on the guidelines. Obviously, the ERAS team needs to have the full support of the hospital administration and heads of departments and the support from their colleagues to lead this new way of working. Continuous control of the care process is introduced through enrollment of every consecutive patient into an information technology (IT)-based interactive audit (based on the ERAS® Guidelines) performed by the team on a regular basis. And at the core, ERAS ensures patient involvement in their own care and recovery. Lastly, but not least, ERAS is not a fixed protocol—it is a new way of working. It is about building a readiness to make changes. Surgery and anesthesia care are constantly developing, and that requires continuous updating to run the most modern and best care protocols.

Evidence-Based Protocols

ERAS® care is based on information that is available in the medical literature. The aim is to find information that can help improve the outcomes for patients undergoing surgery. The focus is on reducing complications and ultimately mortality and supporting the return of normal function and well-being of the patient while also taking cost into account. Academic expert scholars in the field review and grade the knowledge in the medical literature in a systematic way and build an evidence-based guidance for perioperative care. This usually consists of somewhere between 15 and 25 different care items depending on the operation (www.erassociety.org for updated and free available guidelines on many major surgeries).

Evidence based means that the evidence has been assembled and graded to inform the reader how good the best evidence available is. It does not guarantee that the evidence is of high quality by default and gives no promise that the care item recommended has the highest evidence. All it states is that the level—unavailable, fair, good, or strong—has been assessed and is presented. This grading is coupled with a second assessment, this time on the potential risks of harm by the treatment. Together these two factors are weighed by the experts to give a graded recommendation for each item.

The protocol aims to find all care elements and actions that impact the recovery and outcomes of the patient's care. It starts from the first meeting with the patient and covers the entire journey, ending with a follow-up and audit no sooner than a month after surgery (Fig. 1.2). Every single element—be it screening for anemia or malnutrition and subsequent actions depending on the findings, to the choices of surgical

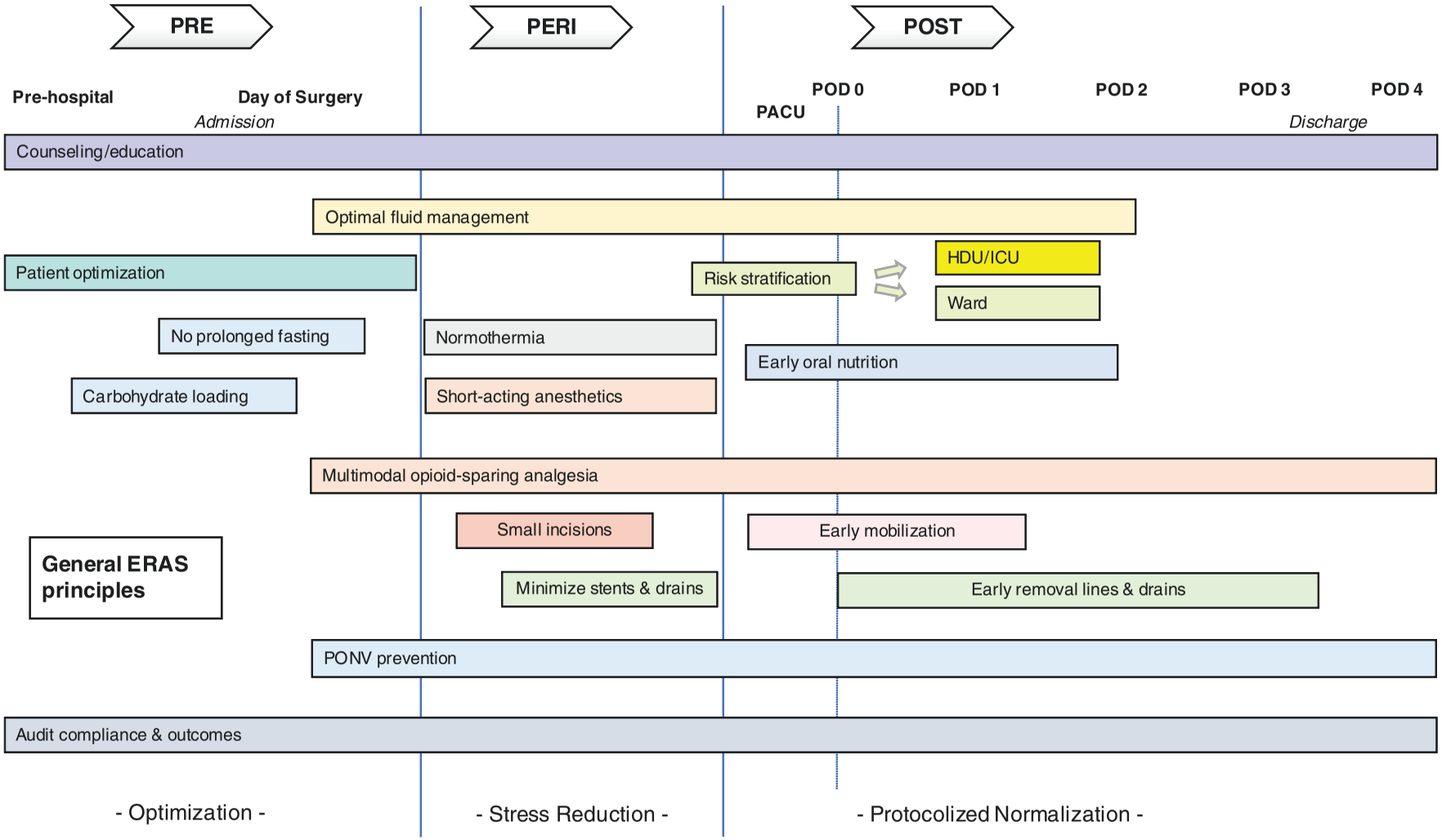

Fig. 1.2 General ERAS principles. PACU postanesthesia care unit, HDU high-dependency unit

approach or anesthesia, to care elements such as early feeding—is included as long as they have support in the literature for improving outcomes (see Fig. 1.2).

Are some elements in an ERAS protocol more important than others? When reviewing the patient's journey and the elements that have an impact on outcomes, it quickly becomes evident that all specialties and professions involved in the care of the patient have elements on the list. Some units might think that a certain element is standard of care and argue that only a few of the list of elements in an ERAS® guideline are true elements that need to be in an ERAS protocol. While this is probably true for that unit, the neighboring hospital will most likely not have the exact same view about what is standard of care. For them another set of the elements may apply. When moving between countries and regions, this becomes even more obvious. In fact, there is solid data to show that the variation in care delivery comes down to the individual doctor delivering the care [11]. This variation in care delivery is probably the leading cause of the differences in outcomes between hospitals, countries, and regions.

What has been shown repeatedly is that with increasing use of the care elements recommended by the ERAS® Society Guidelines, outcomes improve substantially. With an increase in compliance from 50% to above 70% with the colorectal protocols, several reports from different units show a reduction in complications by 25–30% and length of stay by several days (30–40%) [14–16]. Depending on the unit and their specific practice, different care elements were found to be the most important. This informs us that it is hard to single out one or two elements from the entire protocol as always being the most important, since the main factor determining this is related to what the local practice is when introducing all elements of the protocol.

The ERAS Team

The ERAS team is the core of having ERAS in place in a hospital unit. Because it is a completely new and different way to run care, it has to have the full support of the management/administration, heads of departments, and other decision makers.

All professions and specialties need to be represented on the team to ensure successful implementation of the ERAS protocol. The team should secure that there is at least one member covering every unit engaged in the care of the patient. This includes a surgeon, an anesthesiologist and pain and recovery specialist, nurses, physiotherapists, and dietitians. These specialties form the core ERAS Team for each surgical department and always in collaboration with anesthesia and post-op care. The team collects key data on every patient and meets on a regular basis (weekly or biweekly). The team makes medical decisions to align their local practices with the guidelines to form a local protocol. Nurses, physician assistants, dietitians, and physiotherapists add their insights and knowledge to help form the practicalities of the local program. This team forms the core of the entire transformation the unit is doing to continuously improve care and to sustain changes and improvements made. The task of the team is to lead ERAS processes and changes in the care of the patients. They do so by getting control of practice and outcomes using audit as a core tool.

Audit

In some countries it is mandatory, or at least expected, to report to national or regional quality registries for many surgeries. These registries are very common in northern Europe and in North America. They typically report back to each participating unit on an annual basis. The report typically shows the results for every participating hospital or unit while benchmarking against all others. These results include mortality, complications, practice, patient demographics, and other basic information. Many of them are also used for research with the inclusion of all patients, thus reflecting current practice. Quality registries represent a very important step in the development of national quality improvement projects and have been shown to help improve practice outcomes. The weakness of quality registries is that the data reports what happened at least 1 year ago. In many cases, they are focused on the specialty interest and may miss out on reporting factors that may also influence the outcomes reported (see above surgery and anesthesia). Analysis is done retrospectively, and it remains uncertain if the data entered was done in a prospective or retrospective fashion. Nevertheless, these registries have played a major role in the development of surgery and anesthesia and continue to do so.

From the start, the ERAS® Society aimed to further develop audit by introducing the ERAS® Interactive Audit System (EIAS) [17]. The idea was to develop a system that could be used in a more direct way on a regular weekly basis by allowing almost immediate feedback on outcomes. It also aimed to secure that all processes involved in outcomes are captured and integrated into the analysis. This allows for the clinical ERAS team to understand why they may have certain outcomes and direct actions to change practice where it is failing to improve outcomes. The system is built on the ERAS® Society Guidelines, but it also includes definitions of outcomes based on a number of international societies' definitions and grades severity of the complications using the Clavien classification to tell what level of care was instituted [18]. The system is built to be swift and allow the team to instantly access all their data in an interactive semi-live way.

Since the data collected comprises all elements needed for a quality registry, it serves as an introduction in countries that do not have it. In addition, it also comprises all the elements that are recommended to include in studies of ERAS [19], and as such the system is also built to be used for research.

The ERAS team can use the audit tool to give feedback to every unit involved in the care pathway. This information should typically include the overall outcomes for the patients but also the processes behind the outcomes and the compliance to the guidelines. This helps the team to understand everyone's role in the bigger picture. Many complications occur not only because of just one missed or failed treatment. Instead most complications often arise from several poorly or mis-performed treatments in the care pathway. This demands the actions of several units to maximize the impact to reduce the occurrence of a given complication. This is why the audit needs to cover all care choices that impact outcomes and that it is being measured for every patient in near real time. This allows for better targeted actions and immediate follow up for all involved to see how well they are doing and an effective way of studying the impact of changes made.

Reporting

A very important factor in raising the quality of care in complex organizations is to involve as many people as possible. To have the entire staff engaged and working in the same direction will allow for substantial improvements in just about any hospital.

While it may seem trivial, reporting on outcomes and processes to the entire staff in a department of surgery or anesthesia on a regular basis is often a completely new feature. While many units struggle to meet economic needs and secure hospital beds when in shortage—this and other similar problems are the focus—the actual outcomes of the care are less often reported. This is an overlooked way of managing the exact same problems and actually of much higher intrinsic value for the staff performing the care. Many units implementing ERAS have shown that it reduces cost substantially by improving the outcomes of care [20–23].

Still, the experiences from implementation of ERAS in different parts of the world show the same picture: In the teams of doctors and nurses trained for ERAS, just about nobody knows the outcomes of the care delivered in their own unit, and when asked to estimate the results, most are overly optimistic. It is common that the members of the ERAS team starting their training underestimate the complication rates and the length of stay by about 30% or more. When asked about how well they are performing ERAS, the compliance to the guidelines is also substantially lower than what is found when consecutive patients are assembled and audited. Most units start with a compliance rate of 40–45%. The truth of where the problems and the poorly performed care elements lie demands a strict and continuous audit. What is not measured remains unknown.

This example is even more true for the rest of the staff who are delivering the care on a daily basis. To get the engagement of the staff, data is extremely helpful to make things change for the better. Professionals in healthcare have often chosen this line of work to help their fellow men and women. If there are ways that leadership can support this ambition, it is nearly always most welcomed. Therefore, one of the most important tasks is to report to everyone on a regular basis and to help them see how they can improve the recovery and care of their patients. The ERAS team also should report to management, as this is a way of showing value to them for the investment they have made by giving the team part of their valuable time to run and lead ERAS. Anyone who has experienced the transformation of the patient from a traditional care pathway to ERAS will immediately recognize the difference. This is the best payback for all involved, not least the staff on the floor.

Readiness to Change

The ERAS team is developed to lead continuous change. Surgery and anesthesia change all the time. And one change in a certain part of an ERAS protocol may result in many more changes to follow. One example is the change from open to minimally invasive surgery. This not only changed anesthesia drastically but also pain management, mobilization, and a range of other care items along the initial ERAS care pathway. It is important to understand that ERAS is not a protocol that is static. On the contrary, ERAS is a way of constantly updating best practice with new knowledge and care plans. Surgical units and departments being prone to change and staying informed of the latest improvements via updated guidelines and that use clever IT systems to audit their practice will improve their chances of always staying and using the best available care.

The Next Steps in ERAS

There have been substantial improvements in surgery and anesthesia over the years, and many of them have involved monitoring or technical improvements. ERAS is bringing these improvements together by adding the softer aspects to the table: communication and teamwork. But it also brings in an element of something missing for a long time: basic information needed to run the improvements in care—useful audit for everyday purposes. This has been missing until now.

Because of the economic pressure and an unsustainable rise in cost of healthcare, new ways of sustaining cost or decreasing it and yet developing care have to be found. To date few innovations in surgery can match the cost savings from ERAS. Repeated reports have shown savings of thousands of dollars from implementing ERAS even when taking all investments in personnel and IT and other support into account. This is likely to be an important factor for the continuous growth and spread of ERAS around the world.

Another opportunity that is being developed is the collaboration in large and growing groups of ERAS hospitals to work together in clinical research. By using the platform of the common IT system, a worldwide platform is spreading and allowing for immediate collaborations on various projects. Already a large number of studies have been produced using this system, and more are underway.

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Physiology and Pathophysiology of ERAS

2

Thomas Schricker, Ralph Lattermann, and Francesco Carli

Introduction

In the development and implementation of the enhanced recovery after surgery (ERAS) program, there has been the need to understand the mechanism and the factors that affect the recovery process. Most of the elements considered by the ERAS® Society to have an impact on recovery have a physiological basis, and the interaction between them characterizes the modulation of the stress response. For example, besides surgical incision, some of them such as pain, hemorrhage, immobilization, and quasi starvation have a synergistic effect. The activation of the sympathetic system and the inflammatory response associated with all these surgical elements characterize the surgical stress response (Fig. 2.1), thus leading to a state of low insulin sensitivity, which represents the most important pathogenic factor modulating the perioperative outcome.

The low insulin sensitivity of the cell is characterized by an abnormal biological response to a normal concentration of insulin, the latter being responsible to control the metabolism of glucose, fat, and proteins. Therefore, a change in insulin sensitivity as a consequence of surgery impacts the whole metabolism. It results in an alteration in glucose metabolism with increased hepatic glucose production and decreased peripheral uptake leading to hyperglycemia. In addition, there is a breakdown of proteins at whole-body and muscle levels. These are the main metabolic characteristics of the surgical stress response.

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The increased endogenous glucose production is correlated to the increased protein breakdown, and more precisely the breakdown into amino acids was shown to be directly responsible for the increase in hepatic endogenous glucose production. As there is a strong association between these two metabolic alterations and the postoperative rate of complications, it is plausible to assume that low insulin sensitivity can represent the main pathogenic mechanism.

This chapter covers the pathophysiology of glucose, insulin, and protein metabolism and the clinical relevance within recovery. Additionally, the chapter explores the attenuated response to surgical stress by the various elements of ERAS.

Glucose Metabolism

Pathophysiology

Fasting plasma glucose levels are normally kept between 3.3 and 6.4 mmol/L. Maintenance of normoglycemia is the result of a well-regulated balance of hepatic glucose production and tissue glucose uptake. Surgical stress triggers the release of counter-regulatory hormones (catecholamines, glucagon, cortisol, growth hormone) and pro-inflammatory cytokines (tumor necrosis factor-alpha [TNF-α]; interleukins: IL-1, IL-6), which lead to a state of insulin resistance. As a result, we observe a stimulated glucose production rate accompanied by decreased body glucose utilization causing an increase in the circulating blood glucose concentration (Fig. 2.2a–c).

The hyperglycemic response to surgery has long been recognized to depend on the type, severity, and extent of tissue trauma. Minor surgery is not associated with a clinically relevant increase in glycemia [1]. In fasting patients undergoing elective intraperitoneal procedures, however, blood glucose levels typically increase to 7–10 mmol/L. During cardiac surgery, mainly due to the profound inflammatory alterations

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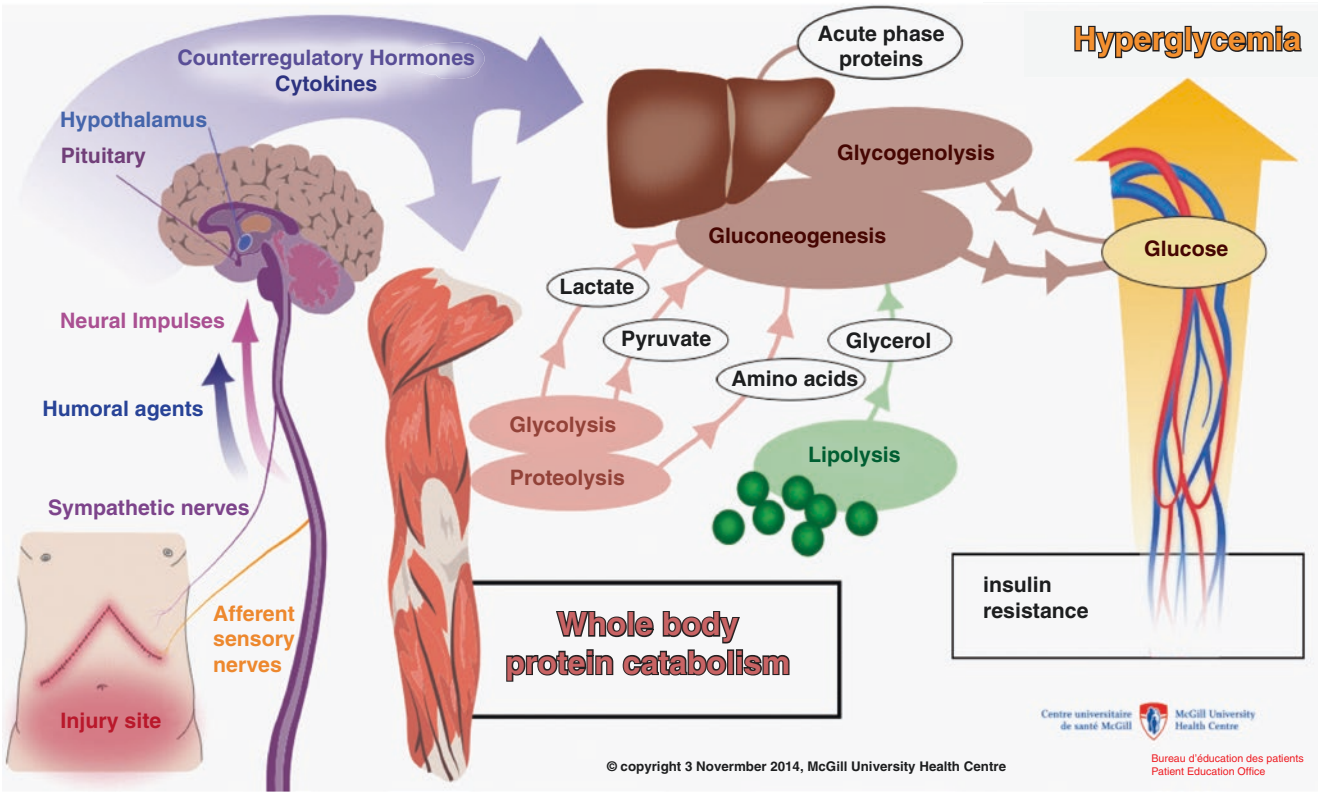

Fig. 2.1 A rise in circulating glucocorticoids, catecholamines, and glucagon (i.e., counter-regulatory hormones) is elicited by activation of the hypothalamic-pituitary-adrenal axis and sympathetic nervous system. The response is mediated by afferent nerves and humoral factors including cytokines generated from the site of injury. Mobilization of energy reserves promotes hyperglycemia and catabolism. Hyperglycemia develops as a consequence of insulin resistance coupled with an inappropriately high hepatic glucose production. Proteolysis and lipolysis accelerate to provide precursors for gluconeogenesis. The resultant amino acid efflux also supports the synthesis of proteins involved in the acute-phase response. (Reprinted with permission from Gillis and Carli [1])

associated with cardiopulmonary bypass, the disturbance of glucose homeostasis is severe, with glucose values frequently exceeding 15 mmol/L in nondiabetic and 20 mmol/L in diabetic patients.

Although the effect of surgical technique on glucose metabolism has not been widely studied, laparoscopic procedures may have less impact than the open approach. Possibly mediated through the reduction of tissue damage and the inhibition of inflammatory responses, patients following laparoscopic colon resection showed better glucose utilization when compared with laparotomy [2].

The choice of anesthetic drugs also is important. While intravenous anesthetics, such as propofol, appear to have no effect, inhalational agents are capable of impeding pancreatic insulin secretion. In contrast, opioids, particularly when administered in large doses, and neuraxial techniques mitigate the hyperglycemic response to surgery.

Perioperative use of corticosteroids, even in small doses, for the prevention of postoperative nausea and vomiting, as well as catecholamines, intravenous drugs, diluted in 5% dextrose,[1] blood products, and parenteral feeding exacerbate hyperglycemia, even in the absence of diabetes mellitus [3].

There is evidence to suggest that a large number of patients show abnormal glucose homeostasis before surgery. In a prospective study in 500 patients presenting for elective procedures, 26% of previously undiagnosed patients demonstrated blood glucose levels in the impaired-fasting glucose or the diabetic range [4]. Only 10% of diabetic patients in this observational study presented with a normal blood sugar prior to the operation.

Assessment

Accurate, precise, and timely measurement of blood glucose is an essential element of modern perioperative care. The circulating blood glucose concentration can be assessed using

[1]Please note: the infusion of a 100 ml bag of dextrose 5% (=5 g of glucose) almost doubles the amount of circulating glucose in a 70 kg nondiabetic patient (assuming a glycemia level of 5 mmol/L = 0.9 g/L and a blood volume of 77 ml/kg) [5].

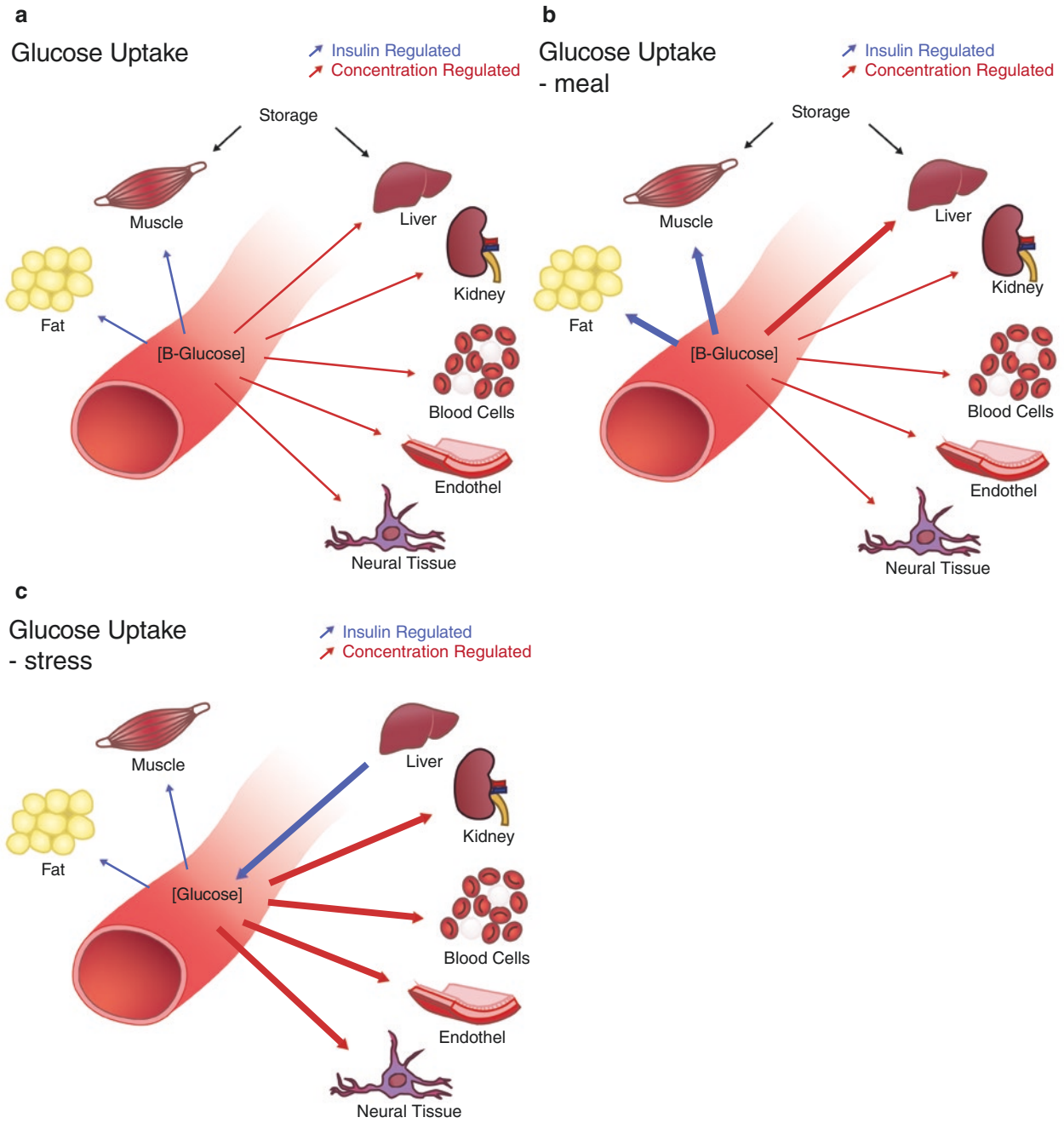

Fig. 2.2 (**a**) Glucose uptake. (**b**) Glucose uptake following a meal. (**c**) Glucose uptake during stress

laboratory serum and plasma glucose analysis, whole blood and capillary glucose measurement by blood gas analyzers, or glucometers. Glucose analysis in the laboratory, the gold standard [6], may not provide results fast enough to promptly and effectively treat hypo- or hyperglycemic episodes in the operating theater. Hence, perioperatively glycemia is being routinely assessed by so-called point-of-care (POC) devices such as glucometers and blood gas analyzers. Blood glucose results obtained by older POC devices in the acute critical care setting need to be interpreted with caution, mainly because they do not correct for hematocrit [6–8] or other confounders such as body temperature, pH, pO_2, tissue perfusion, hypoglycemia, and various medications [6]. Although the advent of newer technologies provided more reliable data

in the critically ill [9], no studies addressed limitations and accuracy of glucometers during surgeries provoking the most profound alterations of glucose homeostasis. Hence, not unexpectedly, there are no clear recommendations by the US Food and Drug Administration (FDA) regarding specific glucometer safety requirements for patients warranting intravenous insulin therapy perioperatively.

In 2017 the use of the Nova StatStrip® Glucose Hospital Meter System in patients undergoing different types of surgery showed 100% accuracy of capillary and arterial glucose values based on the International Organization for Standardization (ISO) 15197:2013 criteria, i.e., all values were within zones A and B on the Parkes error grid for type 1 diabetes mellitus [10]. However, neither capillary nor arterial blood glucose results met the Clinical and Laboratory Standards Institute (CLSI) POCT12-A3 guidelines as required for intensive insulin protocols aimed at stricter glycemic control.

Results of a more recent study demonstrate that arterial blood glucose measurement by StatStrip® in cardiac surgery was accurate before the initiation of cardiopulmonary bypass (CPB) but lacked accuracy during and after CPB—most likely due to the interference of heparinization and anemia.

Clinical Relevance

Traditionally, the hyperglycemic response to surgery has been regarded as adaptive and beneficial because it ensures continuous provision of glucose for tissues that are glucose dependent, i.e., brain, erythrocytes, and immune cells.

Surgical stress, however, triggers the release of mediators that, on one hand, inhibit the expression of the insulin-dependent membrane glucose transporter glut 4, which is mainly located in the myocardium and the skeletal muscle, and, on the other hand, stimulate the expression of the insulin-independent membrane glucose transporters glut 1, 2, and 3, which are located in blood cells, the endothelium, and the brain (Fig. 2.3).

As insulin-dependent cells appear to be protected by insulin resistance, most of the circulating glucose enters cells that do not require insulin for uptake resulting in a cellular

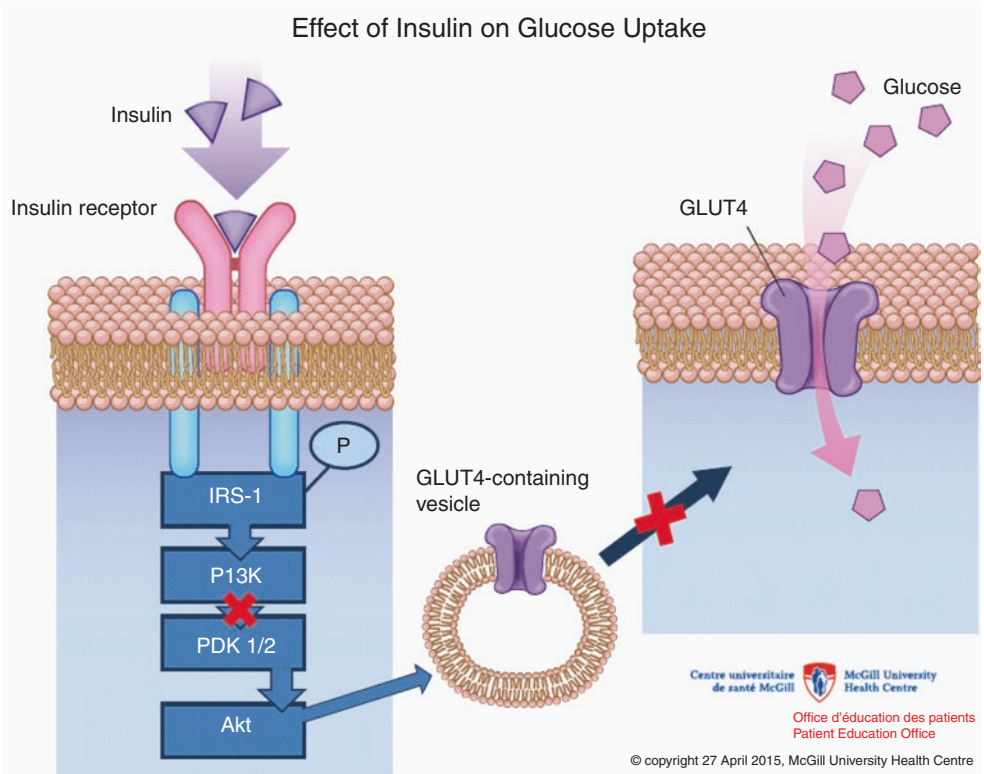

Fig. 2.3 In the healthy postprandial state, glucose concentration rises, and the subsequent increase in circulating insulin activates intracellular signaling cascades that ultimately result in the translocation of glucose transporter type 4 (GLUT-4) to the plasma membrane. Following elective surgery, hormonal and inflammatory mediators generated by the surgical stress response produce a state of insulin resistance. A reduction in peripheral insulin-mediated glucose uptake is observed and believed to be the cause of (1) a defect in insulin signaling pathways, particularly phosphoinositide-3-kinase-protein kinase (P13K) or (2) a defect in the translocation of GLUT-4 to plasma membrane. *Akt* serine/threonine protein kinase, *IRS-1* insulin receptor substrate 1, *P* phosphorylation, *PDK1/2* 3-phosphoinositide-dependent protein kinase 1. (Reprinted with permission from Gillis and Carli [1])

glucose overload. Once inside the cell, glucose either nonenzymatically glycosylates proteins such as immunoglobulins and renders them dysfunctional or goes into glycolysis. That pathway generates excess superoxide radicals, which by binding to nitric oxide (NO) promote the formation of peroxynitrate that ultimately leads to mitochondrial dysfunction and apoptosis.

Hence, a growing body of evidence indicates that even moderate increases in blood glucose are associated with adverse outcomes after surgery [11]. Patients with cardiovascular, infectious, and neurological problems appear to be particularly sensitive.

In general surgical wards, patients with fasting blood glucose concentrations above 7 mmol/L or random blood glucose levels >11.1 mmol/L had an 18-fold greater in-hospital mortality, a longer stay, and a greater risk of infection than patients who were normoglycemic [12]. Acute hyperglycemia has been linked to an increased incidence of surgical site infections after cardiac procedures [13] and total joint arthroplasty [11], allograft rejection after renal transplantation [14], and functional deterioration following cerebrovascular accidents [15].

Hyperglycemia presumably contributes to increased mortality in patients after myocardial infarction [16], stroke [17], open heart [18], and general surgery [19]. Acute hyperglycemia—via manipulating nitric oxide synthase activity and the angiotensin II pathway—limits vascular reactivity and suppresses the immune system by inactivating immunoglobulins and inhibiting neutrophil chemotaxis/phagocytosis.

Acute changes in glucose levels may facilitate the development of post-traumatic chronic pain. In a chronic post-ischemia pain animal model, hyperglycemia, at the time of injury, increased, while strict glycemic control reduced mechanical and cold allodynia [20].

More recent evidence, mainly based on observational studies, indicates that perioperative hyperglycemia may increase the incidence of postoperative delirium and cognitive dysfunction in adults [21]. In children operated on for congenital heart problems, postoperative hyperglycemia had no effect on neurodevelopmental outcomes after 4 years [22].

Marked fluctuations in blood glucose may be harmful independent of the absolute glucose level [23]. Increased magnitudes of perioperative glycemic changes in patients undergoing elective coronary bypass surgery were associated with a greater risk of atrial fibrillation and length of intensive care unit (ICU) stay [24].

However, there is not a consistent definition of glycemic variability, and several metrics (e.g., the coefficient of variation of blood glucose levels or the glycemic lability index) have been used in critical illness. It also remains unclear whether variations within the normal glycemic range or periods of significant hypo- and hyperglycemia are problematic.

There is evidence to suggest that the quality of preoperative glycemic control is clinically important. Elevated levels of plasma glycosylated hemoglobin A (hemoglobin A1c), an indicator of glucose control in the preceding 3 months, were found to be predictive of complications after abdominal and cardiac surgery [25, 26]. In non-cardiac, nonvascular patients, preoperative blood glucose levels above 11.1 mmol L^{-1} were associated with a 2.1-fold higher risk in 30-day all-cause mortality and a 4-fold higher risk of 30-day cardiovascular mortality [27]. In a large cohort of 61,536 consecutive elective non-cardiac surgery patients, poor preoperative glycemic control was related to adverse in-hospital outcomes and 1-year mortality [28]. Diabetic patients undergoing open heart surgery with a HbA1c > 6.5% had a greater incidence of major complications, received more blood products, and spent more time in the ICU and the hospital than metabolically normal patients [29].

Insulin Metabolism

Pathophysiology

Insulin is the chief anabolic hormone in the human body. Although most recognized for its role in regulating glucose homeostasis, insulin plays a pivotal role in promoting protein synthesis and inhibiting protein breakdown. It is less known that insulin exerts non-metabolic effects including vasodilatory, anti-inflammatory, anti-oxidative, anti-fibrinolytic, and positive inotropic effects with potential clinical impact [30, 31].

Insulin resistance can be defined as any condition whereby a normal concentration of insulin produces a subnormal biological response. This umbrella term may comprise states of insulin insensitivity, insulin unresponsiveness, or a combination of both. Although the terms insulin sensitivity and insulin responsiveness are often used interchangeably, their difference stems from the classic sigmoidal dose-response curve of insulin action [32]. Insulin sensitivity is characterized by the insulin concentration required to achieve a half-maximal biological response, whereas insulin responsiveness is defined by the maximal effect attained. Impaired insulin sensitivity is, therefore, represented by a rightward shift in the insulin-dose response curve, and decreased responsiveness corresponds to a height reduction of the curve.

Proper use of these terms is important because they reflect different defects in insulin action: Insulin insensitivity appears to be more implicated in alterations at the pre-receptor and receptor level, whereas decreased responsiveness is related to post-receptor defects [32].

With regard to glucose metabolism, surgical patients should be called insulin insensitive because normoglycemia

(= biological response) can be achieved by using large enough quantities of insulin. Whether similar relationships exist concerning the pharmacological effects of insulin on immunological and cardiovascular parameters or its anti-catabolic role in protein metabolism remains to be studied.

Much of the impairment of insulin function after surgery can be explained by the stress-induced release of counter-regulatory hormones. These hormones exert catabolic effects, either directly or indirectly, by inhibiting insulin secretion and/or counteracting its peripheral action. The observed association between the time course of perioperative interleukin 6 plasma concentrations and insulin resistance suggests that inflammatory mediators are also involved [33].

The main site for surgery-induced insulin resistance is skeletal muscle, because this is the quantitatively most important organ for insulin-mediated glucose uptake. The magnitude of whole-body insulin resistance is most pronounced on the day after surgery (up to 70% reduction) and lasts for about 3 weeks after uncomplicated elective abdominal operations. It has been primarily linked to the invasiveness of surgery [34]. Other factors may also contribute, such as the duration of trauma [35], bed rest and immobilization [36], type of anesthesia and analgesia [37], nutrition and preoperative fasting [37, 38], blood loss, physical status, and post-surgery rehabilitation [39].

Assessment

The gold standard for the assessment of insulin resistance in humans is the hyperinsulinemic-normoglycemic clamp technique, whereby insulin is infused at a constant rate to obtain a steady-state insulin concentration above the fasting level [40]. Based on frequent measurements of plasma glucose levels, glucose is intravenously infused at variable rates to maintain normoglycemia. Given that endogenous glucose production by the liver and kidneys is completely suppressed, the glucose infusion rate (under steady-state conditions) is reflective of glucose disposal and is, therefore, an indicator of peripheral insulin resistance: The greater the glucose infusion rate, the more sensitive the body is to insulin and vice versa.

Other indices traditionally used to quantitate insulin sensitivity in patients, such as the homeostasis model assessment (HOMA) index, the quantitative insulin-sensitivity check index (QUICKI) (both based on plasma insulin and glucose levels), or oral/intravenous (IV) glucose tolerance tests, have shown to be only poor indicators of insulin function.

Recent observations suggest that body mass index (BMI) and the quality of preoperative glycemic control (hemoglobin A1c) may be simple predictors of insulin sensitivity during major surgery [29, 41].

Clinical Relevance

Studies performed over a 6-year period in Sweden in the early 1990s demonstrate a significant correlation between the degree of the patient's insulin sensitivity on the first postoperative day and length of hospital stay [33]. More recently a significant association was reported between the magnitude of insulin resistance during cardiac surgery and outcome [29]. Independent of the patient's diabetic state, for every decrease in intraoperative insulin sensitivity by 20%, the risk of a serious complication including all-cause mortality, myocardial failure requiring mechanical support, stroke, need for dialysis, and serious infection (severe sepsis, pneumonia requiring mechanical ventilation, deep sternal wound infection) more than doubled after open heart surgery [29].

These findings lend support to the previously held contention that, perioperatively, alterations in glucose homeostasis are better predictors of adverse events than the presence of diagnosed or suspected diabetes mellitus itself. The outcome relevance of insulin resistance is also reflected by the problems associated with its metabolic sequelae, i.e., hyperglycemia and protein wasting, the "diabetes of the injury."

Protein Metabolism

Pathophysiology

Normal protein metabolism is characterized by an equilibrium between anabolic and catabolic pathways. Surgical stress leads to biochemical and physiologic perturbations of neuroendocrine homeostasis, including stimulation of the sympathetic nervous system, parasympathetic suppression, and activation of the hypothalamic-pituitary axis (Fig. 2.4) [42].

This results in a mobilization of substrates in order to improve the chance of survival. Metabolic pathways are shifted from anabolism toward catabolism [43]. Skeletal muscle protein stores are mobilized to provide amino acids for two main purposes: first, the amino acids can be converted to glucose by the liver as an energy source during a hypermetabolic state, and second, they serve as substrate for protein synthesis by the wound and the liver.

Typical features of protein catabolism are stimulated rates of whole-body protein breakdown and amino acid oxidation. The synthesis of rapidly turning over acute-phase plasma proteins is also upregulated; however, it is not to the same extent as protein breakdown, resulting in a net loss of functional and structural body protein [44–47]. Metabolically healthy patients lose between 40 g and 80 g of nitrogen after elective abdominal surgery, equivalent to 1.2–2.4 kg wet skeletal muscle [48]. Patients with burns or sepsis experience daily losses of up to 800 g of muscle mass. Protein loss

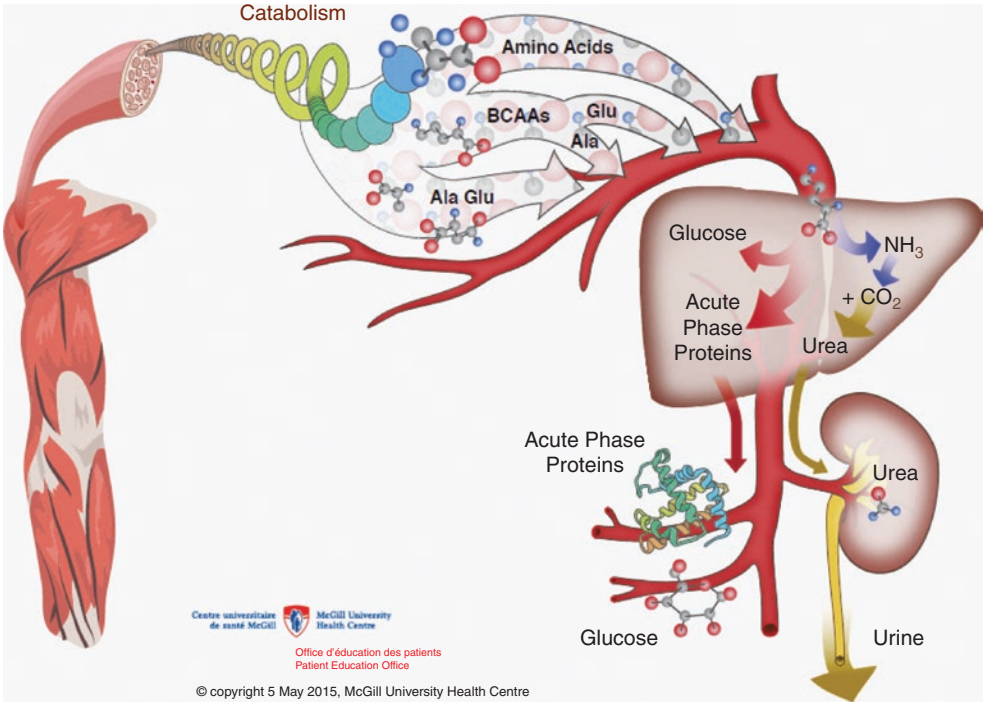

Fig. 2.4 The surgically stressed state is characterized by an elevation in protein turnover (i.e., protein synthesis and degradation), release of amino acids into circulation, urinary nitrogen losses, and impaired uptake of amino acids in skeletal tissue. Lean tissue is catabolized, releasing amino acids into circulation (including glutamine, alanine, and the branched chain amino acids [BCAAs]), while hepatic amino acid uptake is enhanced. This allows for reprioritization of protein synthesis to acute-phase reactants and the production of glucose via gluconeogenesis. Glutamine (Glu) and alanine (Ala) account for the majority of the amino acid efflux from peripheral tissues and are readily extracted from circulation by the liver. The excess nitrogen is converted in the liver to urea by combining ammonia (NH3) with CO_2 (carbon dioxide). Urea is then released into circulation, traveling to the kidneys, where it can be filtered into urine. The BCAAs undergo irreversible degradation in skeletal tissue, in part for synthesis of glutamine and alanine, which reduces availability of these indispensable amino acids for reutilization in protein synthesis. Collectively, these metabolic changes promote whole-body protein catabolism. (Reprinted with permission from Gillis and Carli [1])

in insulin-resistant patients, after colorectal cancer surgery, has been shown to be 50% greater than in patients with a normal insulin response [49]. More recent studies indicate a linear relationship between insulin sensitivity and protein balance in parenterally fed patients undergoing open heart surgery [50].

Muscle wasting occurs early and rapidly during the first week of critical illness and is more severe among patients with multiorgan failure [45]. Significant muscle weakness and physical disability can persist for more than 5 years after injury and critical illness [51, 52].

There is no evidence to suggest that the magnitude of catabolic changes in elderly patients differs from those in younger adults. Age, however, may be associated with reduced muscle mass and a decreased capacity to utilize nutrients. Older patients may, therefore, be more vulnerable to protein catabolism [53].

There are different rates of uptake or release of amino acids in specific regional vascular beds. During the acute phase of injury, amino acids are released from skeletal muscle as a result of accelerated proteolysis. These amino acids are extracted from the bloodstream of the splanchnic bed for hepatic synthesis of structural, plasma, and acute-phase proteins.

Two amino acids, alanine and glutamine, account for approximately 50–75% of the amino acid nitrogen released from skeletal muscle, although they make up only 6% of protein in muscle stores [54]. Alanine is an important glucose precursor and indirectly provides this fuel source, which is essential for several key tissues. Glutamine is a gluconeogenesis substrate but also serves as primary substrate for immune cells and enterocytes, participates in acid-base homeostasis, and serves as a precursor for glutathione, which is an important intracellular antioxidant. It has been hypothesized that the tissue requirements for glutamine may outstrip the ability for tissue (particularly skeletal muscle) to produce this amino acid. Hence a relative deficiency state exists, characterized by a fall in glutamine concentrations in both the plasma and tissue compartments [55].

The plasma concentration of albumin, a so-called negative acute-phase protein, typically decreases in response to surgical stress. Studies measuring the synthesis rate of albumin,

however, provide more insight into the underlying mechanisms. While the synthetic rate of albumin decreases during surgery, it is upregulated during the early postoperative period and only returns to normal values after several weeks [56]. The physiologic significance of albumin synthesis and its regulation in patients undergoing surgery need to be further investigated. While under normal conditions, increased amino acid availability represents an important regulator of protein synthesis, it seems that in postoperative patients, other factors (inflammation, endocrine stress, and liver function) also play important roles [57, 58].

Bed Rest and Fatigue

Confining patients to bed for a prolonged period of time initiates a series of metabolic responses that can be deleterious if not corrected. Both muscle weakness and atrophy begin after only 1 day of bed rest, with the extent being greater in older people [59].

Malnourished Patients

Malnourished cancer patients experience a higher morbidity and mortality in response to surgical treatment, have a higher hospital readmission rate, and have a prolonged convalescence when compared with those who are normally nourished [60, 61]. Clinical outcome studies suggest that sarcopenic patients benefit more than their normal counterparts from a short course of intravenous nutrition, particularly if initiated before surgery [62–64]. Total parenteral nutrition in catabolic, depleted patients with gastrointestinal cancer, after trauma and during sepsis, resulted in a greater reduction of net protein catabolism than in nondepleted patients [65, 66].

In order to evaluate the efficacy of nutritional support, the patient's baseline catabolic state must be quantified because sarcopenia is related to postoperative morbidity and mortality [61, 67]. A significant association exists between the degree of preoperative catabolism and the anabolic effect of nutrition, with catabolic patients benefiting the most [68]. These more recent observations support the previous demonstration of superior outcomes in perioperatively fed malnourished patients [64].

Assessment of Catabolism

Many clinical and biochemical indices have been used to characterize the nutritional status of surgical patients, but all techniques have limitations [69–71]. Anthropometric and body composition measurements need to be treated with caution in subjects who are dehydrated and/or have edema or ascites [69]. Serum proteins are pathophysiological markers influenced by factors other than malnutrition or catabolism, such as inflammation with redistribution and dilution [69, 72].

Protein economy in surgical patients has traditionally been characterized by measuring nitrogen balance, i.e., the difference between nitrogen entering and exiting the body. Nitrogen is mainly lost in the form of urea, which represents about 85% of the urinary nitrogen loss. This proportion, however, has been shown to vary widely. Because of the fixed relation between protein and nitrogen (1 g protein contains 6.25 g of nitrogen), urinary nitrogen excretion has commonly been assessed as a surrogate marker of whole-body protein loss. However, urinary nitrogen excretion measurements are unable to address the question of whether muscle wasting is a result of increased proteolysis, impaired protein synthesis, or, simply, the lack of proper anabolic response to nutrition. Furthermore, retention of nitrogen within the body and underestimation of nitrogen excretion in urine and other routes (feces, skin, wound secretion) invariably lead to false positive values [73, 74].

Tracer methods using amino acids labeled with stable isotopes (^{2}H, ^{15}N, ^{13}C) are considered the technique of choice for the global assessment of catabolism in humans and its relation to protein and energy intake [75]. They provide a dynamic picture about the kinetics of glucose and amino acids on the whole-body (protein breakdown, oxidation and synthesis, glucose production and utilization) and organ tissue level [76–78].

Clinical Relevance

Because protein represents structural and functional components, the loss of lean tissue delays wound healing, compromises immune function, and diminishes muscle strength after surgery [79, 80]. The ensuing muscle weakness prolongs mechanical ventilation, inhibits coughing, and impedes mobilization, thereby causing morbidity and complicating convalescence [81, 82]. The length of time for return of normal physiologic function after discharge from the hospital is related to the extent of lean body loss during hospitalization [82].

Significant mortality occurs after critically ill patients are discharged from the ICU and hospital [51]. Many of these deaths are ascribed to the loss of muscle mass, inadequate physical activity, muscle weakness, and the inability to mobilize.

Metabolic Attenuation of the Stress Response

The pathophysiology of the surgical stress response is multifactorial, and therefore the therapeutic interventions should aim at identifying those metabolic components within the perioperative trajectory. Conceptually, the treatment of postoperative, low insulin sensitivity will normalize insulin action and the main components of metabolism. The implementation

of several metabolic modalities and their use in an integrated fashion modulate the perioperative establishment of the state on insulin resistance, also called low insulin sensitivity.

Perioperative Nutrition

With the fed state insulin levels elevated, storage of substrates is made available, and insulin sensitivity is elevated in anticipation of the incoming stress. There is sufficient evidence that preoperative carbohydrate drink increases insulin sensitivity before surgery and attenuates the establishment of insulin resistance in the postoperative state [83]. Complex carbohydrates appear to have a greater insulin secretion response, which would have a pronounced effect on blocking gluconeogenesis.

The physiological advantage of feeding at time of catabolic stress is the stimulation of insulin production, which inhibits protein breakdown and facilitates the incorporation of supplied amino acids into protein synthesis [84].

Anabolism, a positive whole-body protein balance, is required for optimal patient recovery after surgery. Patients undergoing major elective surgery present with a negative whole-body protein balance, generated from an increase in proteolysis, as early as the first postoperative day [85, 86]. Therefore, the primary goal of perioperative nutritional care is thus the provision of protein to attenuate catabolism, as well as maintenance of normoglycemia, adequate hydration, and avoidance of fasting [87]. The extent to which anabolism is accomplished depends not only on the medical care provided, including ERAS, but also on the timing, route of delivery, and composition of the nutritional support regimens provided.

Insulin Therapy

Insulin sensitivity, rather than insulin responsiveness, is reduced throughout the period of surgical stress, probably as a result of the raised inflammatory response that affects insulin target cells. Insulin therapy is suggested when normoglycemia and protein balance need to be maintained. The perioperative administration of insulin to maintain blood glucose between 6 and 8 mmol/L is recommended in order to overcome postoperative insulin resistance and improve outcome [88].

Minimally Invasive Surgery

Activation of inflammatory pathways that could negatively impact on the recovery process can be reduced by limiting either the size or the orientation of the incision. Endoscopic techniques limit the size of the incision and the trauma to the abdominal wall by splitting the muscle fibers instead of cutting them. Changing the incision from vertical to horizontal could also decrease pain as a result of having less dermatomes involved in transporting nociceptive signals to the central nervous system. In addition, inflammation can be reduced by minimizing internal organ manipulation and direct peritoneal injury and blood loss [89].

Neural Deafferentation

Administration of epidural and spinal local anesthetics initiated before surgery and maintained during the first 48 hours after surgery (epidural only) has been shown to decrease perioperative insulin resistance, to attenuate the decrease in muscle protein synthesis and the rise in blood glucose, and facilitate the anabolic effect of amino acids in type 2 diabetics [90, 91]. The addition of nutrition while on neural blockade promotes protein synthesis and improves postoperative protein balance.

Maintenance of Intraoperative Normothermia

Maintaining patients normothermic during surgery has been shown to attenuate the perioperative release of catecholamines and decrease loss of body nitrogen [92]. Although no data on the metabolic effect of normothermia on insulin sensitivity are available, it is plausible to associate mechanistically the sparing protein loss process with improved insulin sensitivity.

Physical Activity and Mobilization

Long-term bed rest and sedentary activity produce marked changes in glucose and protein metabolism [93, 94]. Two weeks of limb immobilization has been shown to decrease the quadriceps lean mass by almost 5% and the strength by 25% and lowers peripheral insulin sensitivity [95].

Elderly and frail patients are particularly vulnerable, since loss of muscle mass impacts on their functional strength and functional capacity [96]. There is sufficient evidence that exercise training improves glucose metabolism and particularly insulin sensitivity. This is particularly evident in diabetic patients. The anabolic effect of exercise training can be enhanced by adequate intake of amino acids. Mobilization after surgery should therefore be considered an important factor in achieving anabolism, and this can be facilitated with adequate analgesia.

Conclusion

While we are aware of the implications of low insulin sensitivity associated with surgery on body metabolism, the connection between physiological and clinical outcomes is not always demonstrated.

The relative role of different pathogenic mechanisms in the development of postoperative insulin resistance leading to higher morbidity needs to be clarified. Hopefully, this can lead to better understanding and future therapeutic strategies. This implies that more work needs to be done to fill the gaps between what we know and what we do in clinical practice. Patients will be the ones who will gain from these advances in research and clinical care.

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Guidelines for Guidelines

3

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What Are Guidelines?

Clinical guidelines are documents sanctioned by national boards, specialist organizations, or government stakeholders to assist clinicians with medical decision-making on various aspects of healthcare [1, 2].

They are developed by specialists, patients, and other experts through a systematic review of the relevant literature. This peer-review process should be performed in a manner that minimizes bias while providing full transparency on recommendations [1, 2]. They should be written in a way that is possible for both clinicians and patients to understand and interpret [3].

The resulting evidence-informed recommendations can be used to address a variety of clinical questions, including guidance on the assessment, investigation, and management of specific clinical conditions, and in setting quality standards [4]. Recommendations for areas of future research may also be made.

Why Is There a Need for Guidelines?

The management of most clinical conditions involves deciding between multiple options for assessment, investigation, and management [5–8]. While considerable evidence may be available on these aspects of healthcare, it can be very difficult to filter through this information and provide the best advice to individual patients [9]. Guidelines offer potential solutions based on systematically reviewed evidence and recommendations achieved through expert consensus [6, 8].

The resulting documents can be used to support shared decision-making with patients and facilitate service provision. In addition to providing information on risks, benefits, and efficacy of investigative and therapeutic modalities, guidelines can also offer valuable information on cost-effectiveness and resource management for trusts and stakeholders. This information can be used to improve the consistency of care, set gold standards, and provide endorsements where appropriate [1].

Who Is an Expert?

An expert is an individual with specialist knowledge in their field who can effectively weigh available evidence and understand the aspects of implementation when considering the value of any specific recommendation. The specialty knowledge may be from credential qualifications, the study of evidenced research, or clinical experience.

A number of experts from a number of bodies are involved in the formulation of guidelines. Non-clinicians, patients, and laypersons are also regularly involved to provide patient and caregiver perspectives and provide evidence on the appropriateness and acceptability of guidelines for patients [10].

Experts involved in guideline development:

- Relevant healthcare specialty representatives (e.g., surgeons, oncologists, cancer nurse specialists, gastroenterologists, radiologists)

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- Professional bodies, including national organizations
- Service users, i.e., patients and caregivers
- Researchers, e.g., systematic reviewers, epidemiologists, and statisticians
- Health economists
- Patient and clinician stakeholders

Developing a Guideline

Scoping the Guideline

Scoping is one of the most important steps in guideline development. It defines the purpose and scope of the guideline identifying the need it addresses, its target audience, and its potential impact and importance. A steering group should usually be involved in this initial scoping process and in setting up the Guideline Development Group (GDG) [6–8].

Scoping involves an initial literature review to identify relevant existing guidelines and identify priority areas [9]. The scope process subsequently informs the targeted literature searches performed by the GDG and therefore involves the process of setting key inclusion and exclusion criteria and identifying target outcomes.

Guideline Development Groups

Once the need for a guideline has been identified in the scoping process, its ongoing development and finalization is undertaken by the GDG. The GDG consists of a panel of experts whose role is to identify and review relevant evidence from a literature review and propose recommendations in response to the questions raised in the initial scope.

There are no limits to the size of a GDG. However, each member will provide some level of expertise in their own right. Each GDG will have set roles within the group. These may include a chairperson, clinical experts, technical experts, lay-members (patients and/or caregivers), and a project manager. While administrative health partners or healthcare commissioners are not normally invited as GDG members, representatives from health boards or commissioning bodies are required occasionally.

Members are required to attend all meetings, if possible, and are usually selected to be representative of the population relevant to the guideline being formulated. The appointment of GDG members is through competitive advertisement and interview by a governing body such as a National Collaborating Centre (NCC) or the National Institute for Health and Care Excellence (NICE). However, other means of selection of members may be used. GDG members are also required to declare all conflicts of interest relevant to the guideline under development [11].

Although all members of the GDG may share co-authorship and joint responsibility for formulating recommendations for the final guideline, not all members are involved with the process of selecting and reviewing the available evidence or physically writing the guideline. In addition all co-authors should fulfill the criteria for authorship as described in the Committee on Publication Ethics (COPE) guidelines (https://publicationethics.org/authorship).

Patient and public representatives in the GDG ensure that guidelines not only demonstrate equality across different populations but are considerate of a patient's needs including feasibility, burden, and comprehensibility.

Literature Search

Search criteria identified during the initial scoping stage are subsequently used to develop clear, well-constructed questions to aid evidence identification and review by the GDG. In guidelines where interventions are considered, the commonly used PICO (Population, Intervention, Comparator, and Outcome) framework [12–14] is often used to help formulate clear review questions and aid systematic review of the evidence (Table 3.1).

For each review question formulated, a separate systematic review is identified where available or performed where not available. Depending on the scope of the guideline, there may be some value in rapid/modified systematic reviews to aid in feasibility. A separate search strategy should be created for each question. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [15] should be followed for each question including a systematic search of the literature, screening for study inclusion, defined data extraction, and study quality assessment. For feasibility, guidelines with multiple recommendations can be developed using a series of focused systematic reviews with limited searches supplemented with snowballing and citation searching.

Table 3.1 PICO (Population, Intervention, Comparator, and Outcome) framework. A method to aid formulation of the research question and aid systematic review of the literature

Population	Which patient population is being studied?
Intervention	Which treatment or intervention is being recommended?
Comparator	Which alternative treatments are available?
Outcome	Which end points are being studied?

Analyzing Evidence Quality

To minimize bias, the selection of evidence identified from literature searches is based on previously agreed inclusion and exclusion criteria as developed during the scoping stage.

Evidence identified from systematic reviews in guideline development is assessed for quality. The quality of the data provides a basis for the strength of any resultant recommendations [16].

There are many different methods for assessing the quality of evidence. The quality assessment method devised by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) working group is widely used and an excellent tool for evidence quality assessment used in guideline creation [9, 17–19]. The GRADE approach classifies evidence on a scale of 1–4 (Table 3.2). In contrast with alternative grading systems, GRADE is used to provide a quality assessment of the combined literature used to support recommendations rather than individual studies [8].

Although randomized controlled trials (RCTs) are generally deemed to have the higher level of evidence than non-RCTs, the GRADE approach also accounts for additional influential factors, specifically measures that reflect the confidence that the effect estimate is close to the true effect. These include estimates of the risk of bias, measures of consistency, directness, precision, publication bias, and other factors that are not typically used to assess quality, including exposure-effect relationships, large effect measures, etc. This approach also accounts for the fact that a well-designed non-RCT study may provide more relevant and higher-quality evidence than a less relevant or poorly performed RCT [17].

Table 3.2 GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) working group: quality of evidence

Level of evidence	Assigned GRADE quality	Description
1	High	High confidence that the true effect is close to the estimate of the effect
2	Moderate	Moderate confidence in the effect of the estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
3	Low	Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
4	Very low	Very little confidence in the effect estimate

Table 3.3 GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) working group: assessment of recommendations

Strength	Definition
Strong	When *desirable* effects of intervention clearly outweigh the *undesirable* effects, or clearly do not
Weak	When the trade-offs are less certain—either because of low-quality evidence or because evidence suggests desirable and undesirable effects are closely balanced

Strength of Recommendations

Similarly, recommendations following a GRADE review of evidence are also rated as either strong or weak based on a number of influential factors (Table 3.3) [17–19]. In addition to the magnitude of effect of the presented evidence and the quality of the evidence, recommendations also take into account cost-effectiveness and the treatment burden for patients [16, 17].

The Role of Delphi Processes

Different methods of obtaining consensus have been used over many years. The Delphi process is one such method. It was first described by Helmer [20] following its use in the US Army project "Project RAND" (https://www.rand.org/about/glance.html). Since then it has had a number of uses in guideline and policy development.

What Is a Delphi Process?

A Delphi process is an organized method used to achieve expert consensus. It typically involves the distribution of structured questionnaires to a panel of experts, who are asked to anonymously answer questions and weight and justify their responses. The process usually undergoes several rounds and iterations favoring a reduction in the number of correct options at each round, to encourage experts to find consensus. This process is particularly useful when deciding upon recommendations to include within a guideline and determining the strength of those recommendations.

Maintaining Guideline Quality

Guidelines should be developed and reported according to the highest standards of quality. The AGREE II (Appraisal of Guidelines Research and Evaluation II) [21] instrument describes the parameters required to ensure guidelines meet the necessary criteria to provide a reliable resource. It also

provides a template against which existing guidelines can be assessed. In addition, to assess the quality of the guidelines themselves, the limitations of specific guidelines with respect to population, outcomes, and stakeholder interest should also be considered by end users [2].

The Need to Update Guidelines

As guidelines are based on the most contemporary research, it is imperative that guidelines are given appropriate timelines for review. Failure to review accordingly can result in the continued use of incorrect and out-of-date recommendations.

The ERAS® Society Guidelines and Recommendations

The ERAS® Society has followed the aforementioned principles to formulate a series of guidelines to help inform perioperative care. Multidisciplinary and multi-professional expert groups were formed for several areas of surgery, and the evidence available was examined to determine what interventions could be incorporated into best practice to improve overall patient care and outcomes.

The ERAS Study Group (the forerunner to the ERAS® Society) published the first consensus recommendation for care of the patient undergoing colonic resection in 2005 [22]. This paper opened up a completely new view on the care of surgical patients by amalgamating elements of care for the entire patient journey. It included elements that were typically covered in anesthesia guidelines or in guidelines for surgeons or nutrition care. For the first time, elements across the surgical journey found to have an impact on the outcomes were included in one single guiding document. This was a completely new type of guideline and involved all specialties and healthcare professions caring for the patient.

This proved to be a very successful concept. Enhanced Recovery After Surgery (ERAS® Society) guidelines were tested in clinical practice and proved to be very useful. With each additional element adhered to, outcomes improved in a stepwise manner. This was shown in a single institution first by Gustafsson et al. [23] and later in 13 hospitals from 7 different countries [24]. This finding linking ERAS compliance with improved outcomes has since been reported from several units around the world, most recently in 80 hospitals across Spain [25]. All studies report the same principal finding—better compliance to the guidelines results in improvement in several key outcomes: complications, both major and minor, faster overall recovery, and shorter hospital stay. What may differ between the studies are the care elements that made the difference in the improvements, indicating that most if not all the elements may contribute to the outcomes depending on the starting point of the unit where the study was performed. Gustafsson et al. also reported 5-year survival improvement associated with increased compliance in 900 consecutive patients undergoing colorectal cancer surgery [26].

The Guidelines have also been used in organized efforts to implement ERAS (see Chaps. 59 and 60 for details). The UK National Health Service (NHS) was the first to use the Guidelines in a national effort, with several of the leading ERAS units in the country lecturing and presenting their protocols [27]. In the Netherlands more than 30 hospitals underwent a structured implementation program using Breakthrough methodology, which involves more active coaching of teams and a very structured system to drive change in healthcare units [28].

Over the years, an increasing number of surgical specialties have adapted and adopted ERAS® Society Guidelines. Currently, there are 24 ERAS® Society Guidelines (including updates, see Table 3.4) covering various surgical specialties and subspecialties [22, 29–50]. For example, patients undergoing gynecological surgery also have been shown to have improved outcomes with better compliance to an adapted ERAS guideline in a recent paper [51]. In many specialties ERAS principles are still relatively new, and ERAS-specific literature is scarce for many specialties. One of the goals for producing a consensus or a guideline in ERAS-naïve specialties is to get a complete overview of what knowledge is available and where the gaps may be. This will help direct future research efforts. Overall, in a rapidly growing body of literature, better results are increasingly reported across a broad number of surgical procedures when employing ERAS principles. The ERAS® Society provides platforms for these groups to develop specific guideline and research communities. The ERAS® Society also helps these new groups test and validate their guidelines and support leading centers to move the benefits of ERAS to a growing number of patients.

Table 3.4 ERAS® Society Guidelines published in peer-reviewed journals

	Procedures/specialty	Lead author	References	No of citations[a] (18 November 2019)
1	Colonic resection	Fearon KC	Clin Nutr 2005;24:466–77 [22]	673
2	Colorectal surgery	Lassen K	Arch Surg 2009;144:961–9 [29]	598
3[b]	Pancreaticoduodenectomy	Lassen K	Clin Nutr 2012;31:817–30 [30]	227
4[b]	Pancreaticoduodenectomy	Lassen K	World J Surg 2013;37:240–58 [31]	171
5[b]	Colonic surgery	Gustafsson UO	Clin Nutr 2012;31:783–800 [32]	361
6[b]	Colonic surgery	Gustafsson UO	World J Surg 2013;37:259–84 [33]	549
7[b]	Rectal/pelvic surgery	Nygren J	Clin Nutr 2012;31:801–16 [34]	205
8[b]	Rectal/pelvic surgery	Nygren J	World J Surg 2013;37:285–305 [35]	222
9	Radical cystectomy	Cerantola Y	Clin Nutr 2013;32:879–87 [36]	216
10	Gastrectomy	Mortensen K	Br J Surg 2014;101:1209–29 [37]	209
11	Anesthesia for gastrointestinal surgery (Part I)	Scott MJ	Acta Anaesthesiol Scand 2015;59:1212–31 [38]	86
12	Anesthesia for gastrointestinal surgery (Part II)	Feldheiser A	Acta Anaesthesiol Scand 2016;60:289–334 [39]	154
13	Gynecologic oncology (Part I)	Nelson G	Gynecol Oncol 2016;140:313–22 [40]	128
14	Gynecologic oncology (Part II)	Nelson G	Gynecol Oncol 2016;140:323–32 [41]	115
15	Bariatric surgery	Thorell A	World J Surg 2016;40:2065–83 [42]	85
16	Liver surgery	Melloul E	World J Surg 2016;40:2425–40 [43]	114
17	Breast reconstruction	Temple-Oberle C	Plast Reconstr Surg 2017;139:1056e-1071e [44]	46
18	Reporting of results	Elias KM	World J Surg 2019;43:1–8 [45]	6
19	Esophagectomy	Low DE	World J Surg 2019;43:299–330 [46]	14
20	Lung surgery	Batchelor TJ	Eur J Cardiothorac Surg 2019;55:91–115 [47]	25
21	Colorectal surgery	Gustafsson UO	World J Surg 2019;43:659–95 [48]	29
22	Gynecologic oncology	Nelson G	Int J Gynecol Cancer 2019;29:651–68 [49]	8
23	Cardiac surgery	Engelman DT	JAMA Surg 2019;154:755–66 [50]	3
24	Hip and Knee surgery	Wainwright T	Acta Orthoped Scand 2020;91(1):3–19 [52]	3

[a]From Web of Science™
[b]Published simultaneously in Clin Nutr and World J Surg

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Part II

Preoperative Preparation

Preoperative Fasting and Carbohydrate Treatment

4

Jael Tall and Jonas Nygren

Background

Despite continual improvements in the field of medical science, morbidity is still high following major surgery. The risk of postoperative complications following major surgery is determined by not only surgical or anesthetic techniques but also changes in metabolism. These metabolic changes lead to increased catabolism, significantly increasing the risk of postoperative complications as well as impaired long-term outcomes. Administering preoperative carbohydrate drinks, thus avoiding preoperative fasting, has been shown to attenuate these metabolic changes. We discuss the available evidence supporting the use of preoperative oral carbohydrates (POC) and how this treatment reduces the surgical stress response and consequently improves clinical outcomes.

Perioperative Metabolism and the Role of Insulin Resistance

Elective surgery, as well as othertypes of tissue trauma, induces a release of pro-inflammatory cytokines as well as catabolic hormones (stress hormones) (see Chap. 2) [1]. This catabolic response results in a release of amino acids from protein breakdown and free fatty acids as well as a depletion of glycogen stores. Insulin resistance is an important feature of this shift in metabolism due to the reduced anabolic effects of insulin [1]. Although hyperglycemia is a well-known manifestation of insulin resistance, marked impairments in the effects of insulin on protein and fat metabolism occur accordingly. Under such circumstances, only administration of exogenous insulin enables normalization of glucose, protein, and fat metabolism as previously demonstrated [2].

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Insulin resistance develops, not only in patients with diabetes but also in healthy individuals, following elective surgery. Insulin resistance increases in proportion to the severity of the surgical trauma [1, 3]. Thus, the degree of insulin resistance correlates also to length of hospital stay after elective surgery [1, 3]. Evidence on the clinical impact of insulin resistance was provided in a large randomized trial in surgical intensive care, where maintaining normoglycemia by insulin infusion (4.4–6.1 mM) resulted in a 34% reduction in in-hospital mortality and a 46% reduction in sepsis as compared with conventional treatment (patients given insulin to keep blood glucose below 11.9 mM) [4].

Other interventions associated with surgical treatment, apart from the operation per se, have been evaluated as well. Thus, hypocaloric nutrition (2 L glucose 5% [400 kcal/24 hours]) for 24 hours in healthy volunteers reduced insulin sensitivity by 40–50%, while bed rest for the same length of time had no effect [5].

Fasting Before Surgery

Overnight fasting before surgery is an old tradition, based on the presumed risk of aspiration during anesthesia. Since the 1980s, due to clear evidence from controlled trials, several countries have adopted new clinical routines for patients undergoing elective surgery allowing intake of clear fluids such as water, tea, coffee, and clear juice no sooner than 2 hours before induction of anesthesia [6].

Furthermore, experimental models of severe stress showed markedly worse outcome in fasted compared to non-fasted animals [7]. In light of these findings, it was debated whether fasting was the best way to prepare for surgery.

The concept of avoiding preoperative fasting was initially evaluated using intravenous 20% glucose infusions in several clinical studies involving patients undergoing different types of surgery in order to shift from the fasted to the fed state. In a randomized trial in open elective cholecystectomy, postoperative insulin resistance was reduced by 50% in

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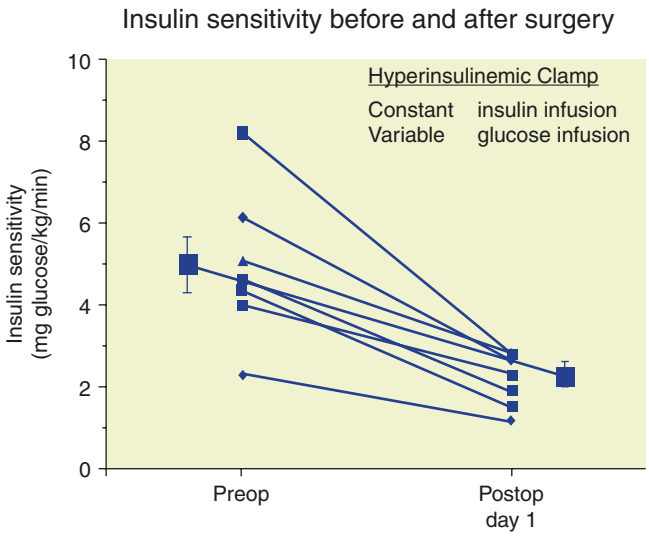

Fig. 4.1 Insulin sensitivity before and after surgery in 7 individual patients undergoing open cholecystectomy

patients given intravenous (IV) glucose (5 mg/kg/min overnight), as compared to patients undergoing the same surgery after an overnight fast [8] (Fig. 4.1). This was in agreement with previous studies after major abdominal surgery showing less postoperative protein losses with insulin treatment [9]. Markedly improved postoperative insulin sensitivity using perioperative glucose infusion was also shown in hip replacement [10]. In this study, glucose and insulin infusion was associated with improved substrate utilization and less increase in cortisol levels, thus further demonstrating an attenuated stress response. Lastly, glucose infusion alone or in combination with insulin before cardiac surgery has repeatedly been shown to improve outcomes, such as arrhythmias and need for inotropic support [7].

Preoperative Oral Carbohydrates

In order to stimulate an insulin response and change metabolism from a fasted to a non-fasted state preoperatively, without increasing the risk of aspiration, a carbohydrate-rich drink with low osmolarity (maltodextrin) to enhance gastric emptying was developed (400 ml [200 kcal], 240 mOsm/l, 12.6% carbohydrates, Nutricia preOp®). The preoperative drink stimulated a satisfactory insulin response, similar to that after a regular meal. Scintigraphic studies in healthy subjects as well as in patients in the morning before elective surgery demonstrated that the drink was completely emptied from the stomach within 90 minutes after intake [11]. POC has been used in several thousand patients participating in studies and in several million patients in clinical practice without significant adverse events being reported to the manufacturers, supporting the safety of the proposed regimen. Safety issues relate to conditions with known or suspected delay of gastric emptying, such as emergency patients, bowel obstruction, or diabetes mellitus. Some data indicate that well-controlled type 2 diabetic patients may receive POC [12], and this is discussed in both ERAS® Society guidelines [13] and in guidelines from the American Society for Enhanced Recovery [14]. Nevertheless, safety issues as well as the potential beneficial effects from POC, and logistics regarding use of antidiabetic medication or insulin in the morning of surgery in conjunction with POC, need to be further studied before a wide implementation can be recommended in this group of patients.

How Do Preoperative Carbohydrates Work?

The Metabolic Response to Preoperative Oral Carbohydrates

In previous clinical studies, POC has been recommended as a dose of 800 ml (400 kcal) in the evening before surgery and a repeated dose of 400 ml (200 kcal), 2 hours before initiation of anesthesia. The effect of POC on postoperative insulin resistance was evaluated by the use of hyperinsulinemic euglycemic clamps in patients undergoing elective surgery. Thus, all patients were evaluated before as well as after surgery and served as their own controls with regard to the response to surgery. In two clinical trials, insulin sensitivity was found to be less reduced after POC by approximately 50% in patients undergoing colorectal surgery [11] as well as hip replacement surgery [15]. Although a Cochrane review [16] clearly demonstrated significant effects from POC on postoperative insulin resistance, there are a few negative studies reported. A clamp study in patients 2 days after orthopedic surgery showed no effect of POC on postoperative insulin resistance [17]. Based on previous studies, it is likely that the metabolic effects of POC on insulin resistance seen in the immediate postoperative period may not be sustained several days following minor/moderate surgery in contrast to major abdominal surgery with a more pronounced and prolonged stress response [15]. Another placebo-controlled randomized controlled trial (RCT) in patients undergoing orthopedic surgery, where insulin resistance was measured 3 days postoperatively, showed that although no difference in whole body glucose disposal was found (Fig. 4.2), POC attenuated the postoperative increase in endogenous glucose release (Fig. 4.3) and reduced nitrogen losses, indicating a persistent significant effect on insulin sensitivity [18].

In a study using protein and glucose isotopes in combination with the insulin clamp, POC improved protein metabolism in patients undergoing colorectal surgery [19]. The study showed that improved whole body glucose disposal was due to a maintained effect of insulin to suppress glucose production in the liver [19]. Several RCTs support an effect

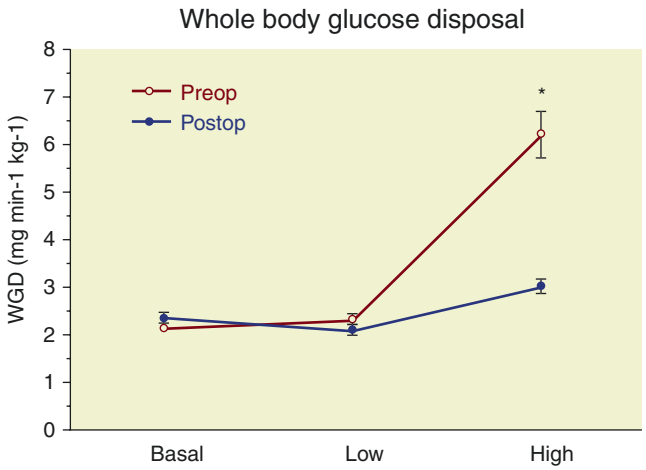

Fig. 4.2 Whole body glucose disposal (WGD)

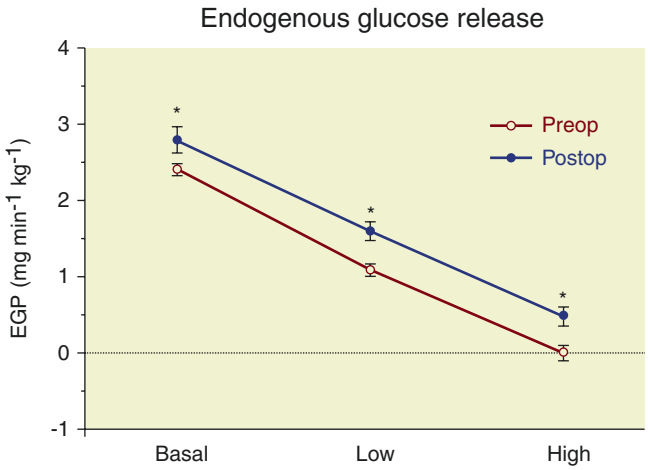

Fig. 4.3 Endogenous glucose release. EGP Endogenous glucose production

of POC on other aspects of the postoperative metabolic response such as protein metabolism, muscle mass, muscle strength, and immunity [1, 20].

To investigate the relative role of the evening vs. morning dose of POC, respectively, for improved insulin sensitivity post-surgery, a study was performed in healthy subjects. POC improved insulin sensitivity by 50% 3 hours after intake (corresponding to the effect of the morning dose), while the dose in the evening before the clamp did not improve insulin sensitivity the following day [21]. This was also later supported by an experimental pig model [22], indicating that it is enough to provide POC 2 hours before surgery to achieve the desired effects on insulin sensitivity resulting in attenuated postoperative insulin resistance (Fig. 4.4). If patients are not allowed to eat and drink freely during the evening before surgery, such as when preoperative mechanical bowel preparation is indicated, the evening dose of POC is probably still beneficial to avoid extended preoperative fasting.

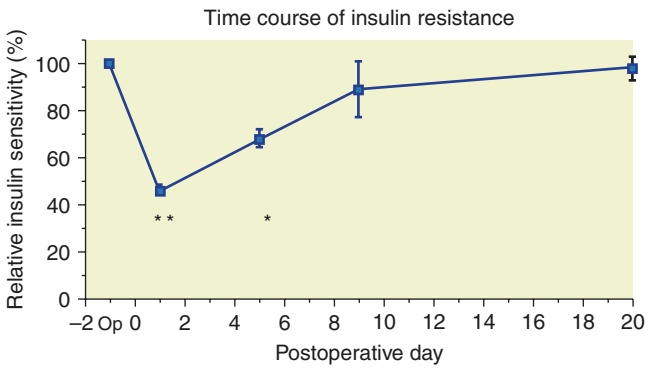

Fig. 4.4 Time course of insulin resistance following open cholecystectomy, ANOVA analysis of variance

Mechanisms Behind Metabolic Effects by Preoperative Oral Carbohydrates

How POC attenuates postoperative insulin resistance still needs to be defined in more detail. Inflammatory pathways in the skeletal muscle [23] as well as in adipose tissue are activated by surgical stress [24], and a relationship between levels of interleukin-6 (IL-6) and postoperative insulin resistance was reported [25]. It is therefore possible that POC might also reduce the inflammatory response to surgery. In addition, surgery impairs insulin effects on glycogen synthase activity and GLUT4 translocation [26]. Furthermore, reduced inflammation as reflected by lower postoperative levels of IL-6 [27] and C-reactive protein (CRP) levels [28, 29] and improved postoperative immune response have been reported after POC administration as compared to after preoperative fasting or placebo administration [20]. In other clinical studies in patients undergoing colorectal surgery, it was shown that improved insulin sensitivity after POC was associated with increased levels of free insulin-like growth factor 1 (IGF-1) (which has proven insulin-like effects), related to increased proteolysis of the major carrier protein of IGF-1 (IGFBP-3) [30–32].

In experimental studies, POC postoperatively reduced free fatty acid (FFA) concentrations and increased oxidative glucose disposal, while neither non-oxidative glucose disposal nor hepatic insulin sensitivity was improved [22]. In a follow-up study in pigs, the same authors reported improved insulin inhibition of Forkhead box protein 01 (FOX01)-mediated PKD4 and protein expression in muscle by POC after surgery, suggesting that POC improves insulin sensitivity by increasing carbohydrate-derived pyruvate flux into the mitochondria [33]. In a RCT in colorectal surgery, POC was related to less reduced postoperative insulin sensitivity, and this was associated with higher levels of muscle protein tyrosine kinase (PTK), phosphoinositide 3-kinase (PI3K), and protein kinase B (PKB) as compared to fasting or placebo [34]. Similar results were also found in patients undergoing

laparoscopic cholecystectomy [35]. In addition, a RCT after radical gastrectomy [36] reported that POC was associated with improved mitochondrial function and less marked structural changes in the mitochondria.

Effects on Clinical Outcome by Preoperative Oral Carbohydrates

The effects of POC were assessed in a recent Cochrane systematic review [16]. Based on 27 trials involving 1976 patients, it was concluded that POC apart from a reduced postoperative insulin resistance also slightly but significantly reduced hospital stay in all patients (mean difference [MD] −0.30, 95% CI −0.56 to −0.04). Since several included studies were performed in minor surgery with short hospital stay, the effect from POC on hospital stay and complications in this Cochrane review were evaluated separately in patients undergoing surgical procedures with an estimated hospital stay of more than 2 days—such as for major abdominal surgery (Figs. 4.5 and 4.6). In this group of patients, a clinically relevant and significant difference in hospital stay of 1.66 days was found (MD −1.66, 95% CI −2.97 to −0.34), while no effects were found on postoperative complications. Importantly, no events due to aspiration have been reported in any of the published clinical trials of POC.

In 2 studies including 86 subjects, return of bowel function was measured, and, in agreement with previous experimental studies [37], a shorter time for return of flatus was demonstrated after POC [16]. Although reported in some studies, [38] no overall effect from POC was found on postoperative nausea or well-being in the Cochrane review. However, in two recent RCTs, POC influenced postoperative nausea and vomiting, pain, and well-being after laparoscopic cholecystectomy [39, 40].

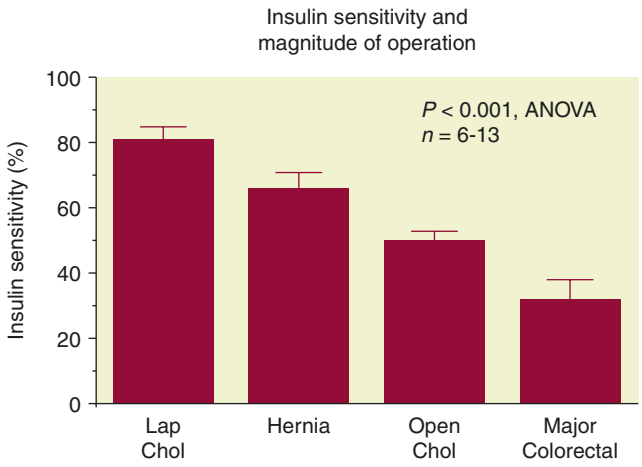

Fig. 4.5 Insulin sensitivity and magnitude of operation

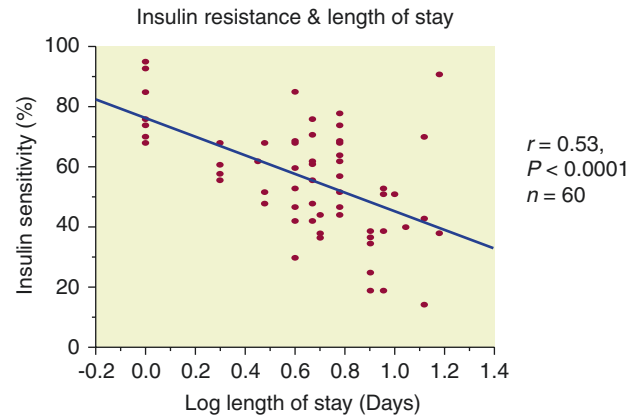

Fig. 4.6 Insulin resistance and length of hospital stay

Preoperative Oral Carbohydrates as a Part of the ERAS Protocol

Enhanced Recovery After Surgery (ERAS) protocols are evidence-based perioperative care protocols aimed to attenuate the metabolic stress response and improve clinical outcomes. Currently, they are widely implemented and a natural part of most guidelines in major surgery [41]. The first ERAS protocol (2005) was based on the preoperative multimodal care protocol as described by Professor Henrik Kehlet [42]. A randomized trial in patients undergoing colorectal surgical procedures in an ERAS program demonstrated that minimized insulin resistance immediately postoperatively by POC, allowed full nutrition without aggravating hyperglycemia and with a markedly improved protein balance [43]. In addition, in a single-center series of 953 consecutive patients undergoing colorectal resections, POC reduced the need for intravenous infusions preoperatively (Fig. 4.7)—a finding associated with improved clinical outcomes [44]. In fact, POC and avoiding fluid overload were the only two items in

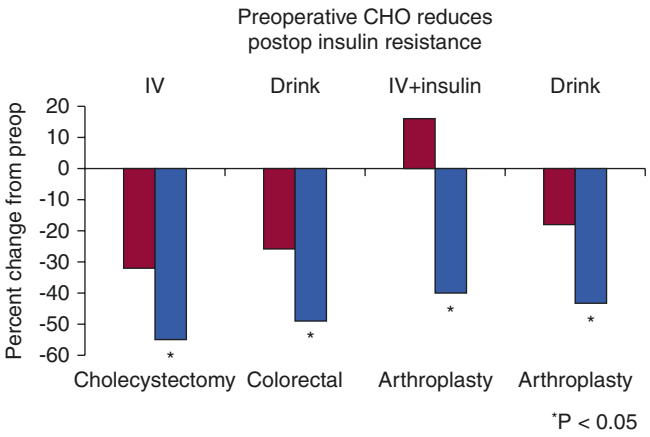

Fig. 4.7 Preoperative carbohydrates (CHO) reduces postoperative insulin resistance. IV = Intravenous administration

the ERAS protocol that significantly predicted clinical outcomes in this multivariate analysis.

Improved outcomes from POC (as a significant predictor of shorter hospital stay) was confirmed also in a large multicenter study using the ERAS® Society database [45].

While the evidence for clinical effectiveness of POC is still weak, a large number of studies indicate that POC plays a significant role to attenuate the postsurgical stress response. Cohort studies indicate that POC contributes to improved patient outcomes in ERAS surgery. Thus, POC is recommended in both the ERAS® Society guidelines [46–48] and guidelines issued by several anesthesiologists' societies [49].

Conclusion

Avoiding preoperative fasting not only improves postoperative metabolism but may also affect clinical outcomes such as return of bowel function and hospital stay. Cohort studies indicate that POC adds significantly to improved outcomes following major surgery when an ERAS protocol is implemented. More studies are needed to further strengthen the evidence on the influence of POC on clinical outcomes. Experimental and mechanistic studies are also important to increase our knowledge on how to best manage and minimize perioperative stress.

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Preoperative Patient Education

5

Jennie Burch and Angie Balfour

Preoperative Education: Rational

There are a number of reasons that preoperative education needs to be undertaken, and these will be briefly examined. A fundamental component of the enhanced recovery after surgery (ERAS) program is the preoperative preparation of patients [1]. This includes physiological optimization as described in prehabilitation and "fit for surgery" programs [2] and also providing psychological support and appropriate information to ensure patients are fully aware of their recovery goals and that they are encouraged to be an integral part of their own recovery. The literature describes the key benefits of preoperative education, which include:

- Reduced anxiety [3, 4]
- Less pain [5]
- Patient compliance in the ERAS pathway, resulting in less complications [6]
- Improved satisfaction [7]
- Improved outcomes [8]

By informing patients about their surgery and their anticipated recovery in more detail, patients should feel more informed and able to contribute to their recovery pathway as they will have been involved in setting realistic goals with the clinical team. Preoperative education allows patients to comply with the ERAS pathway better, thus reducing complications and improving outcomes such as reducing length of hospital stay [9–12].

Patients and their families need to have consistent information from all members of the multidisciplinary team—from the surgeon to the preassessment nurses and ward staff—especially when setting daily goals and realistic expectations about surgical recovery and subsequent discharge planning. One of the criticisms that patients and their families have reported is that conflicting information is given, which can be frustrating and is counterproductive [13].

Another key component of preoperative education is dispelling "myths" that surround recovery after surgery. A lot of patients have either had surgery themselves or know someone who has. This often leads to expectations that are *NOT* realistic.

The rationale for preoperative education is the need to provide key, consistent information, although this may vary depending on the patient's needs such as frailty and cognitive status. Evidence suggests there is a 2-day difference between patients being functionally fit for discharge and them actually going home [14], despite the literature describing a potential reduction in delayed discharges by up to 50% if ERAS principles are applied [15]. Other common reasons for delays are detailed in Box 5.1.

Box 5.1
Common reasons for delayed discharge from hospital:

- Pain
- Weekends
- Staff lacks confidence
- Relative's concern
- Patient lives alone
- Lack of transport
- Lack of social support
- Lack of stoma independence

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Thus it can be seen that preoperative education needs to reduce delayed discharges by appropriately determining the patients' recovery plan, such as social circumstances; e.g., if a patient meets discharge criteria but does not have support at home, it may not be appropriate to discharge the patient at that time. This lack of confidence of staff, patients, or relatives can be avoided by ensuring that preoperative education is delivered to enable patients to have the expectation of going home once they meet the discharge criteria set by the clinical team.

It should not be forgotten that a key component of any ERAS program is the ability to audit outcomes. Collected data includes the delivery of preoperative education, but there is limited evidence to support this crucial element of the ERAS program.

Preoperative Education: By Whom and How?

For best efficacy, patient education about enhanced recovery should occur at the first meeting by the surgical team and continue after the operation. It is not anticipated that the surgical team will have the time within the clinic setting to do more than broach the topic. However, even a brief introduction to enhanced recovery acknowledges to the patient that the whole team is working cohesively, which is essential for enhanced recovery to work [16]. Subsequently, preoperative patient education is frequently the role of the nurse, [17] such as the preadmission nurse or the enhanced recovery nurse.

When a patient was asked about preoperative education, they answered that the healthcare professional made sure "you knew what to expect." [18] Thus it can be seen that preoperative education ensures that patients understand the expectations of them and of the multidisciplinary team.

More than 10 years ago, Billyard and Boyne [19] explained that an important element of the enhanced recovery pathway was provision of preoperative information and optimization. This was enabled within the preadmission clinic and included written information and careful discharge planning. This empowers the patient to become involved in their own care and to take some control over their recovery. Who is to provide this preoperative education is less explicit.

Burch et al. [20] investigated who provided preoperative information about enhanced recovery within the preassessment clinic. This was undertaken using a purpose-designed online survey sent to all the nurse members of the group "ERAS UK," with 37% ($n = 33/89$) returning their responses. A third of these enhanced recovery nurses (39%; 13/33) reported that patient education was one of the key aspects of their role. A quarter of the enhanced recovery nurses (27%; 9/33) undertook preassessment counseling for patients, explaining the principles of enhanced recovery. Thus it can be seen that preassessment is undertaken by healthcare professionals, including the enhanced recovery nurse. It is thought that in some hospitals, after an initial period of training, the existing preassessment team continues the role; and in many hospitals, enhanced recovery is a standard part of the preassessment process. The training of the preassessment team about preoperative education on the enhanced recovery pathway is often the role of the enhanced recovery nurse, as is creating patient education material [21].

Preoperative Education: Delivery Methods

Another consideration is how preoperative education should be delivered. Traditionally, patients attend hospital clinics and are given information about their operation and their predicted recovery plan, but this may not be fit for the purpose.

Preoperative patient education can be delivered in a number of different formats to fit the different requirements of patients, healthcare professionals, and surgical specialties (Fig. 5.1a–c). Traditionally, written information was given to patients about coming into hospital but little was given about how best to prepare for surgery. A variety of other written information is given, but this is usually geared toward the hospital admission itself, including parking costs and visiting hours or providing advice following discharge such as various dos and don'ts and generic dietary advice. However, it needs to be determined if the advice is evidence-based and that appropriate recommendations are being provided to the patients. It is likely that the advice and information being provided need to be reviewed and adapted regularly to ensure that it is fit for the purpose and delivered in a concise, consistent manner. This will enable all healthcare professionals, particularly the nurses delivering the education, to be aware of the evidence surrounding the ERAS program. If patient information is periodically reviewed, updated, and shared with the ERAS team, this will ensure the information being provided is consistent. Furthermore, information should also reflect the activity in the wards, gained from the audit, as opposed to delivering standardized but potentially misleading information.

Traditionally, preoperative teaching is delivered at a preassessment clinic. This is a busy environment, managed by staff that may not have had specific training on ERAS or on education methods. It has been discussed in the literature that the quality of preoperative information given varies between nurses [22]—dependent upon who is delivering the education and their level of experience. Training should be available for preoperative assessment nurses who are teaching patients to ensure that the patients are appropriately prepared for their surgical pathway. Furthermore, to improve patient care, ERAS education should be taught to preregistration nurses [23] and other healthcare professionals.

Before Your Surgery

Preparing for Your Surgery

- ☐ **Exercise** will help make sure your body is as fit as possible before your surgery. If you are already exercising, keep up the good work. If you are not, start slowly adding exercise into your day.
  - Exercise does not need to be strenuous to be helpful; in fact, a fifteen-minute walk is far better than not exercising at all.
  - Refer to the Exercise section (pages 17 to 18) of this booklet to learn what you will need to do after surgery. You can begin practicing these at home.

- ☐ We ***strongly suggest*** you **stop smoking** completely before your surgery, as this will reduce the risk of lung complications afterwards. Doctors can help you stop smoking by prescribing certain medications.
- ☐ **Do not drink alcohol** 24 hours before surgery.
- ☐ **Plan ahead**; make sure everything is ready for you when you go home after your operation. You may need more help at first from friends or family, with meals, laundry, bathing, cleaning, etc.
- ☐ Discharge from the hospital is between two and three days. Tell the nurse as soon as possible if you have any worries about going home. Please remember to **organize transportation** home.

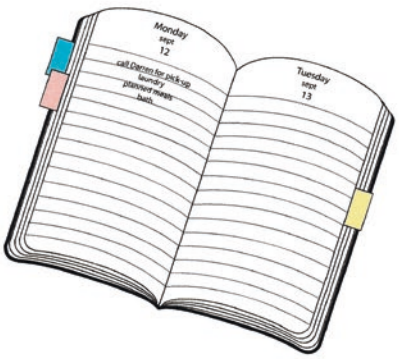

Fig. 5.1 (**a**–**c**) Examples from a patient education booklet that combines written instructions with illustrations to help patients prepare for surgery (http://erassociety.org/patient-information/). (Reprinted with permission from *A Guide to Bowel Surgery*, courtesy of the McGill University Health Centre Patient Education Office, which created the illustrations, design, and layout)

Before Your Surgery

Instructions: Day Before Surgery

Before going to bed, take a shower or bath. Wash your body and wear freshly washed clothes to bed.

You may not eat solid foods, smoke or chew gum after at 02:00, but you are allowed to drink clear fluids up to two hours before your surgery.

Can I eat or drink the day before my surgery?

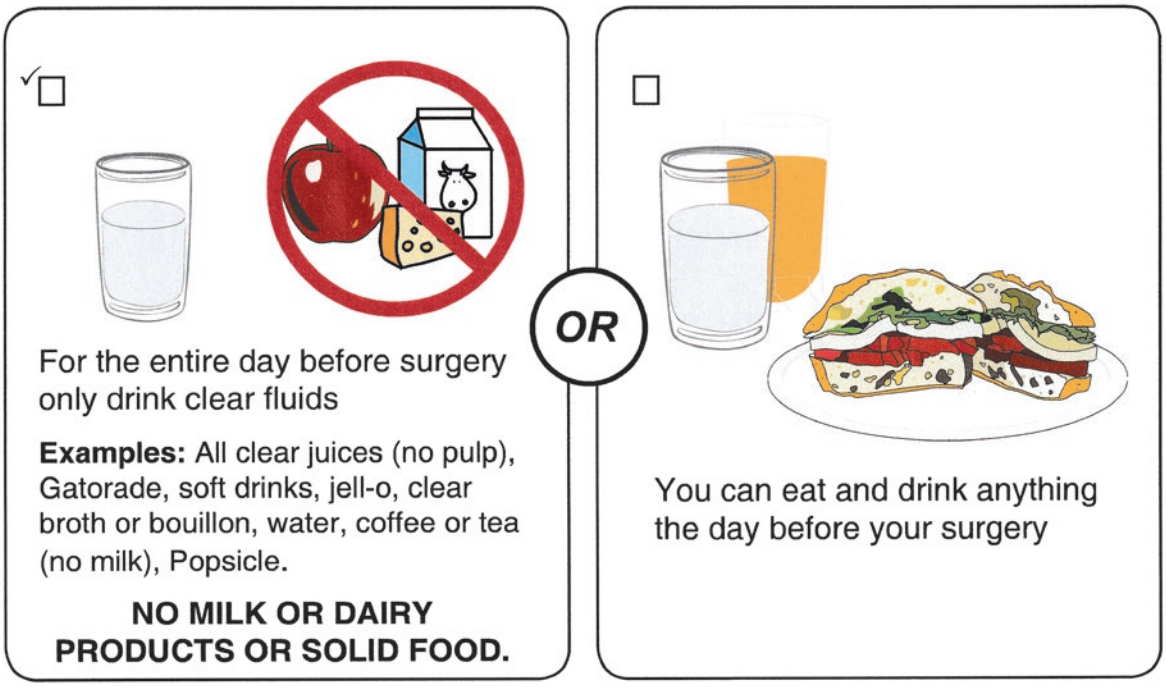

Fig. 5.1 (continued)

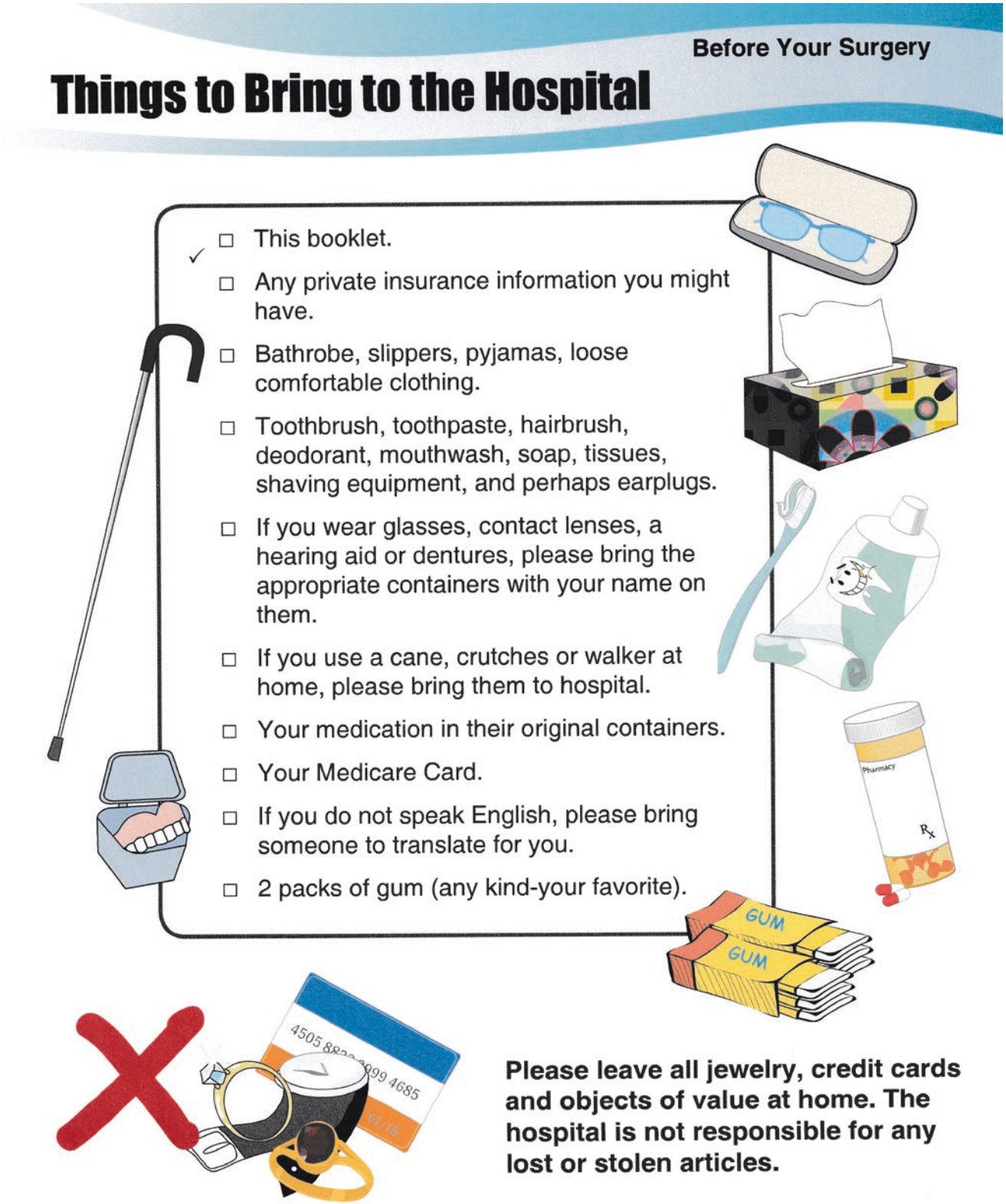

Fig. 5.1 (continued)

Therefore, the traditional preoperative assessment usually undertaken by a nurse within the hospital setting is an element of ERAS that could benefit from a twenty-first-century update. No matter how education is delivered, it may lead to additional time and resources being required in an already stretched healthcare service. In some cases face-to-face preoperative teaching could be replaced by a more efficient and cost-effective process. However, this may be difficult to implement as patients are familiar with the face-to-face approach and may not be keen to change.

Another issue that must be considered when discussing e-health initiatives is the "digital divide":

> …. the vast majority of people in the UK have never heard of 'telehealth' or 'telecare.' Even more significantly, a full 93% of people aged 55 or over (those statistically more likely to be one of the 15 million people in the UK with a long-term condition) had never heard of telehealth or telecare.
> Telehealth Forum, July 22, 2018

Face-to-Face Preoperative Education

Patients report that they would much prefer face-to-face education as opposed to other methods of information delivery; however, this form of education is not always practical and is resource intense and therefore costlier to sustain. Taylor and Burch [18] highlighted one patient comment about forming a "contract" with the nurse. This helped to form realistic expectations as a result of detailed information and the patient reported feeling empowered. If this method of delivery is no longer practical in healthcare settings, alternatives need to be considered that rely less on face-to-face education and more on technology, with the benefit for patients being that they can read more about their recovery after they have left the clinic appointment. This may ensure that preoperative education is more tailored to individuals as patients will be able to read at their leisure and at a level they are comfortable with, although there is the risk that patients may not understand the information and will have no one to clarify it for them.

Written Information

Traditionally, patients were given written materials to prepare them for surgery, but patients have commented that they feel they are given a lot of leaflets and admit to not reading them [24]. The question of health literacy also needs to be considered as not all patients will be able to understand the literature provided. Debbie Watson [21, 25, 26] has published several articles examining health literacy and has emphasized the use of pictorial information as opposed to written information to allow all patients to better understand the information and any relevant instructions, e.g., taking medication or fasting guidelines. Smith et al. [27] concluded in their mixed-methods study that most of the patient education methods they used were rated as "adequate" but did not meet all the needs of the patient.

Cavallaro et al. [28] recently published a study examining the use of scripted preoperative education material and the introduction of a preoperative telephone call from the nurse. They commented on information overload when preparing for surgery and hence the need for a more targeted approach. Their data show a reduction in length of hospital stay and complications and conclude that preoperative education may also reduce costs. This is due to the "buy-in" from patients who are given succinct information and become more involved and ERAS compliant as they understand what they are doing and why they are doing it.

Surgery School

Several units have set up surgery schools to allow patients to meet the multidisciplinary team prior to their admission to hospital. This approach is well established in orthopedic surgery, [29] but little is known about the benefits surgery school may bring to other specialties. One benefit of surgery school is that it allows more than one patient to see the healthcare professional at one time and also enables peer support from other patients.

Digital Information

Some centers have produced DVDs or published online videos describing ERAS. These can be useful but rely upon patients having access to a DVD player or the Internet. Computer or mobile phone apps can also be used to deliver information that allows patients to select how much information they wish to have at any one time. Short videos, for example, can be posted onto platforms such as YouTube, or a link could be added onto the hospital Internet page to enable greater access to such tools. This will allow patients and their families to find out more information when they want and at a pace they are comfortable with. This will avoid information overload that can occur when too much literature is given to patients at one time.

ERAS Nurse

ERAS nurses have been a fundamental component of ERAS from the outset as they add a constant resource to the patient pathway from beginning to end [26]. Ideally, each patient should see an ERAS nurse or preassessment nurse so that ERAS education can be delivered face-to-face for around 20–30 minutes. This approach is labor-intensive and is not

always practical. Another option is that the ERAS nurse produces information and adds it to a Website or app for the patients to access in their own time, with a contact number so they can contact the ERAS nurse to ask questions.

No matter how preoperative information is delivered, it is essential that the patients and their families are given the opportunity to ask questions and discuss any concerns that they may have. It is also essential to provide contact details following discharge, as this part of the journey also can cause anxiety for patients and their families.

There are many potential challenges to providing adequate preoperative education such as lack of resources, but there are also many methods that can be utilized as mentioned above. For ERAS to work it requires patient and staff engagement, with willingness for staff to change any practice that is no longer evidence based or effective.

Preoperative Educational Content

There seem to be a number of essential areas of focus within preoperative education for the patient and their family/caregiver that are required by all surgical specialties. Information should be given orally and additionally either in a written or electronic form to act as a reminder [30–32]. The preoperative education should include [33]:

- Goal setting both preoperatively and postoperatively
- Empowering patients to be self-managing, aiding recovery and potentially avoiding complications
- Information on the surgical and anesthetic procedures [34]
- Exploring discharge criteria and advice

Education should include setting expectations about the operation and daily postoperative goals, with patients being encouraged to play an active part in their recovery. This is confirmed in cardiac surgery by Krzych and Kucewicz-Czech [35] who advocate that information and fitness are both essential in the preoperative period and can help reduce complications and length of hospital stay and promote postoperative recovery.

A number of surgical specialties will be examined in relation to preoperative education. There will also be a brief exploration of prehabilitation, an essential part of preoperative patient education.

Colorectal

There is a larger body of evidence for colorectal surgery than other specialties, as this is where ERAS began. Koh and Horgan [34] consider that stoma education is important to mentally and physically prepare patients and reduce the period of hospitalization. There have been studies advocating the benefits of preoperative stoma training to ensure that when the patient leaves the hospital, they are able to care for their stoma independently. Historically patients were in the hospital for up to 2 weeks, and this enabled the stoma specialist nurse to train patients in the postoperative period. With the benefits of enhanced recovery that include a shorter length of stay, training on stoma care within the hospital setting becomes more difficult. An ideal way to address stoma training is for this to also occur in the preoperative period under the care of the stoma specialist nurse. Chaudhri et al. [36], from the United Kingdom, undertook a small randomized study on patients undergoing elective stoma formation. Half of this group received additional preoperative training, which included two preoperative visits by the stoma nurse to commence self-care training using audio-visual aids. This intervention reduced the time to stoma appliance change proficiency from 9 days to 5.5 days, which is statistically significant. Importantly, there were no adverse effects of the intervention, but there were savings of £1119 per patient. Interestingly, the people who received the preoperative training also had fewer stoma-related nurse interventions after they were discharged home, thus reducing the workload for the community stoma team. Bryan and Dukes [37] subsequently showed how a change in practice enabled patients to become independent with their stoma within 5 days in their small retrospective audit. The change in practice included a preoperative and postoperative structured teaching program. Within the program was an individual practice session in the pre-admission clinic on an abdominal torso and the offer of a further training session. Postoperative changes to teaching included daily postoperative teaching from the first day after surgery. This program reduced the time of stoma independence from 12 days to 5 days, with 60% of patients being discharged home on day 5 or sooner. In a larger study by Younis et al. [38], the authors also concluded that a delayed discharge related to inability to be self-caring with the stoma was significantly reduced with the introduction of preoperative stoma management teaching. These studies show that preoperative stoma training is beneficial in ensuring that patients are self-caring with their stoma prior to discharge home—not only it enables an early and safe discharge home, but also less post-discharge issues related to stoma care were encountered.

Gynecological Surgery

The ERAS® Society guidelines support preoperative gynecological education, due to the potential benefits and the lack of harm, despite limited research [39]. Ituk et al. [31] conducted a study examining patient education in women undergoing caesarean delivery. They conclude that preoperative education should include specific information on a pain management plan and goals for early feeding and mobilization.

Orthopedic

Wainwright and Middleton [29] have explored preoperative education in orthopedic surgery, considering that it needs to correlate to the patient experience once they are in hospital, to remove the element of surprise and increase the patient's confidence. The preoperative education classes for patients and their caregiver should be run by physiotherapists, occupational therapists, and nurses. These sessions should aim to reduce anxiety, provide an explanation of the enhanced recovery pathway, and offer an opportunity to ask questions. Specifically the classes explored preoperative exercises, using crutches, and organizing any equipment required for rehabilitation at home. Furthermore, pain relief and anesthetics were discussed. Place and Scott [40], when exploring the preoperative role of joint schools, consider this to be an excellent modality to manage patient expectations. They consider that joint schools are interactive, multidisciplinary, educational sessions that focus upon preoperative assessment, patient expectations, and postoperative recovery. The authors acknowledge that there is limited effect on length of stay, postoperative pain, or function but consider that it does reduce patient anxiety, and for anxious patients, preoperative education probably improves recovery. Interestingly, Chen et al. [41] have explored costs and reported that preassessment and joint school were £163 of an overall cost of an uncomplicated total knee replacement (£5422) and it could therefore be argued to be an essential and economic component of orthopedic surgery. Galbraith et al. [42] conducted a literature review of preoperative education in arthroplasty and suggested that there are several key components that should be implemented. These include joint school and outpatient consultation to gain consent and set expectations and discharge planning to enable support from social workers or occupational therapists. Additionally, there is a need for physiotherapy involvement as well as a preassessment clinic to assess for surgery and to optimize comorbidities—all are essential components of a successful enhanced recovery protocol. Brennan and Parsons [43] further stated that nurse-led joint schools were best achieved in small groups of four patients and included written information, a take-home DVD, and meeting a patient who has previously undergone the procedure. Thus it can be suggested that preoperative education in orthopedic surgery includes a range of healthcare professionals to facilitate it and needs to be undertaken in small patient groups with verbal and supportive information on recovery to include instruction on exercises.

Thoracic Surgery

Within thoracic surgery, Ardò et al. [32] have explored the nurses' role in providing preoperative education. The authors also discussed physical preparation for surgery and the importance of prehabilitation, which they consider maximizes functional capacity and minimizes postoperative morbidity achieved through control of areas including smoking, alcohol consumption, anemia, and mobility. The latter is enhanced by the physiotherapist providing preoperative education on preoperative exercise, measured by spirometry and ability to climb stairs.

Upper Gastrointestinal Surgery

The recent guidelines for bariatric surgery by Thorell et al. [44] include prehabilitation with the aim of improving functional recovery. Despite a lack of specific literature on bariatric surgery and smoking, the authors recommend cessation for a minimum of 4 weeks, whereas 2 years of abstinence for people with a history of alcohol abuse is considered mandatory, regardless of the limited evidence. Weight loss is also recommended preoperatively for a variety of reasons, including better postoperative weight loss, reduction in liver size, reduction in postoperative complications, and the surgical procedure becoming simpler. They consider that weight loss should be achieved by a preoperative low-calorie diet for 2–4 weeks prior to surgery.

Prior to a laparoscopic cholecystectomy, Blay and Donoghue [45] from Australia have discussed preoperative education by nurses. They reported on a randomized controlled trial of 93 patients comparing standard preoperative education and an individualized education intervention. Neither type of preadmission education was fully explained. However, the intervention group received 30 minutes of verbal education on wound care, diet, activity, bowel management, and managing complications, with the opportunity to ask questions. Plus they received written information on pain management, wound care, diet, and elimination. In addition there was a contact number provided where patients could gain further assistance. The authors reported that although the patients with standard information were satisfied overall with the information they received, they were significantly more likely to request additional information about symptom management than the other patient group. They concluded that verbal and written information improves a patient's ability to self-care after their cholecystectomy.

There is no patient education guidance specific to liver surgery. Melloul et al. [46] advocate the use of patient decision aids, such as printed leaflets and online resources. In addition, they consider that patients should be optimized preoperatively. This preoperative optimization should include oral preoperative nutritional supplementation if needed. In fact, they consider surgery should be delayed for severely malnourished patients to enable weight gain. Optimization for this patient group should also include preoperative mobilization and chest physiotherapy.

Prehabilitation

An important part of preoperative education is prehabilitation. Levett et al. [47] explore the concept of prehabilitation, which will be discussed in greater depth in a subsequent chapter. Prehabilitation can be seen as intervention prior to surgery to improve a patient's psychological and physical status, whereas, traditionally, rehabilitation meant that patients waited until after their operation to improve their fitness. The rationale for prehabilitation is:

- To focus the patient on their impending operation
- To promote behavior change
- To motivate patients to achieve pre-set, personalized goals
- To improve the preoperative functional capacity
- To potentially reduce or prevent postoperative complications
- To provide a focus while waiting for surgery
- To identify and address modifiable factors

Prehabilitation can occur from the decision to operate until the surgery itself. Prehabilitation should include establishment of baselines in functional status, both physical and psychological. Prehabilitation programs are multimodal and multidisciplinary, involving behavioral modification, exercise, nutritional support, and psychological support. Some hospitals have sophisticated Websites to assist patients (such as https://www.erasplus.co.uk/).

In summary although there is limited information on what specifically should be included within preoperative education, in general for all specialties, preoperative education is used to enable patients to increase their knowledge on the topic, to empower them to be involved in their recovery, and to set appropriate expectations. Patient education ideally should explore issues such as stopping smoking and excessive alcohol consumption, as well as physical optimization to potentially reduce postoperative complications and enable a better surgical experience.

Patient's Opinions

The purpose of preoperative education is to prepare patients for surgery. The education that is delivered needs to be fit for the purpose, as assessed by healthcare professionals and patients. Patient feedback should be measured regularly to ensure the ERAS program is working well—not only quantitative outcomes such as reducing length of stay but also qualitative evaluation to examine patients' opinions. The themes that arise from qualitative research about ERAS preoperative education mainly related to explanations and setting expectations for pain, mobility, and length of hospital stay. In general, patients report that they like and appreciate explanation:

- "It was helpful to…discuss my goals and plans".
- "It felt like they were making…sure you knew what to expect" [18].
- "The way he explained it, it seemed straightforward" [48].
- "Get told lots of things about the surgery".

Ninety-four percent (31/34) of patients reported that the preoperative information was "as expected" or "better than expected" [49], whereas for some, the preoperative education was too much:

- "Lots of leaflets and brochures – didn't read them!".
- "Whether my head wasn't in it I'm not sure, but I don't remember being given a lot of face-to-face information on the day and I don't remember particularly reading the information that I was given to take away".

Method of delivery was discussed to be potentially effective in a variety of ways:

- "It was helpful to meet the ERAS nurse before the operation".
- "Some sort of pre-op school… I think that probably would be useful for some people".
- "I think probably the face-to-face stuff is what I'd prefer".
- "Whether an app is helpful, I think probably that would be".

Setting expectations about length of stay was useful to patients:

- "I was pleased that the enhanced recovery pathway meant that I could be out of hospital as quick as possible" [18].
- "I'm a firm believer of being at home rather than in the hospital purely because of the ability to do what I want rather than to be part of a routine" [50].

Having a realistic understanding of pain was also important. In the main, 93% (28/30) of patients when asked about pain said that it was as expected or better than expected after their colorectal operation [49], although good pain control was not always achieved:

- "After the morphine infusion was taken down it was hard to deal with the pain, it felt really intense" [18].

In respect of mobility, 92% (24/26) of patients considered it was expected or better than expected [49]:

- "In fact walking was not too bad" [18].

Thus it can be seen that in general preoperative education is beneficial to set realistic expectations. These expectations can be re-enforced using a patient diary, such as Fig. 5.2, to act as a reminder to the patient in the postoperative period. Furthermore, patients in the main consider preoperative education to be worthwhile, but from their opinions it can be seen that there is no single mode of delivery that patients prefer.

Day One

Drinking

Aim for today: Try and drink about 2 litres (including three supplement drinks). We aim to remove the drip from your arm.

Action: Please list what you have drunk today:

Type of drink	Amount
Water	ml
Juice	ml
Tea/Coffee	ml
Supplement drink	ml
Other	ml
Total amount	ml
Glass of water = 200ml **Tea/ Coffee = 150ml** **Supplement drink = 200ml**	

Progress: If you did not drink 2 litres today, was it due to:

☐ not feeling well ☐ feeling sick

☐ not liking the supplement drinks ☐ other.....

Eating

Aim for today: Try to eat normal foods but smaller portions are often better tolerated. Try eating slowly and chewing your food well.

Action: Please circle how much of food you have eaten today:

Breakfast:	All	Most	Less than half	None
Lunch:	All	Most	Less than half	None
Dinner:	All	Most	Less than half	None
Supper:	All	Most	Less than half	None

Progress: If you have not been able to eat today was it because you were:

☐ not feeling well ☐ feeling sick

☐ not offered food ☐ other.....

Action: Please list any snacks you have eaten today:

.....

Fig. 5.2 An example of a patient diary

Bowels

Aim for today: There is no aim, your bowel function to be a little erratic after your operation.

Action: Please answer the questions below:

I have passed wind	☐ Yes	☐ No
I have had a bowel movement	☐ Yes	☐ No

Getting out of bed & walking

Aim for today: Try and get out for bed for each meal and have 2-4 short walks. Ask for help if needed.

Action: Please circle how many times have you walked today?

1 2 3 4

Action: Please circle how long have you been out of bed today (in total)?

<1 hr 1-2 hrs 2-3 hrs 3-4 hrs >4 hrs

Progress: If you have not been able to get out of bed/walk was it because you were:

☐ not feeling well ☐ not feeling comfortable

☐ not asked to by a nurse ☐ other.....

Exercises & deep breathing

Aim for today: Try to perform your leg exercises and deep breathing exercises as advised.

Action: Please answer the questions below:

I have done my leg exercises as adviced	☐ Yes	☐ No
I have done my breathing exercises as advised	☐ Yes	☐ No

Progress: If you have not done your leg exercises as advised was it because you were:

☐ not feeling well ☐ not feeling comfortable

☐ other.....

Progress: If you have not done your breathing exercises as advised was it because you were:

☐ not feeling well ☐ not feeling comfortable

☐ other.....

Pain and nausea

Are you feeling comfortable (pain well controlled)	☐ Yes	☐ No
Are you feeling nauseous	☐ Yes	☐ No
Have you vomited	☐ Yes	☐ No

Any further thoughts or feelings

.....

Fig. 5.2 (continued)

Conclusion

The subject of preoperative education for surgical patients has very little evidence available in the literature; therefore the information described is frequently anecdotal, and further research is needed to demonstrate clear measurable improvements to patient recovery and outcomes following surgery. Despite the evidence base being weak, the ERAS® Society recommendation for preoperative education remains strong throughout the guidelines that have been published. It appears that there are many different ways to undertake this education and this can vary between specialties, but it ultimately needs to contain a variety of factors that include setting expectations, provision of information on all aspects of the surgical pathway, and patient optimization. Optimization encompasses various health improvement strategies that include exercise and nutrition. Education needs to be provided in a number of different ways to meet the differing needs of patients. Preoperative education should include verbal information as well as written information at a level and format that works for the patient. Education can be given in small groups such as joint school or on a one-to-one basis with the nurse.

Although it seems to be a labor-intensive healthcare episode and it is not without challenges, preoperative education is an essential part of the enhanced recovery pathway and is potentially linked with financial savings and patient benefits. Thus preoperative patient education can be seen as one aspect of the preoperative preparation on the enhanced recovery pathway, with education being provided on a number of topics including the surgical procedure alongside preoperative and postoperative goals. Box 5.2 summarizes a number of points that need to be considered in respect to preoperative patient education.

Box 5.2
A summary of preoperative education:

- Preoperative education enables informed consent, improves patient satisfaction, and promotes patient involvement in their surgical enhanced recovery pathway.
- Patient information can be delivered in a number of ways but must remain person-centered.
- Healthcare professionals must consider the digital divide when introducing e-health strategies to clinical practice.

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Perioperative Optimization of Patient Nutritional Status

6

Stefan D. Holubar and Mattias Soop

Rationale and Scope

Since Dr. Hiram Studley presented his landmark study of increased mortality in patients with marked weight loss before gastric surgery in 1936 [1], surgeons have been aware of the additional risk in their patients who present to surgery with significant malnutrition. Presciently, Dr. Studley concluded that "preparation of those who have lost a good deal of weight, regardless of other appearances in the individual" is essential to improve outcomes [1].

A large proportion of patients undergoing gastrointestinal surgery today remain malnourished [2, 3]. Despite data and guidelines dating from Studley's first study on the subject in 1936, surveys have found that a majority of surgical patients are still not nutritionally screened and many who are at risk of malnutrition do not receive perioperative nutritional support [4]. As optimal postoperative outcomes and attenuation of perioperative stress are key principles in enhanced recovery after surgery (ERAS), recognition and treatment of preoperative malnutrition ideally should be integrated into all enhanced-recovery programs [5, 6].

Definitions

Although early investigation in preoperative nutrition focused on malnutrition, it is now recognized that diseases requiring surgical intervention can be associated with several distinct nutrition disorders. The European Society for Clinical Nutrition and Metabolism (ESPEN) differentiates five main groups of nutrition disorders: malnutrition, sarcopenia, obesity, micronutrient abnormalities, and re-feeding syndrome [7]. Of those, malnutrition and sarcopenia are both common and amenable to intervention in patients awaiting surgery and will be the main focus of this chapter, reviewing the current evidence supporting both enteral and parenteral nutritional supplementation. Overweight and obesity are prevalent in many surgical populations, but are not readily modifiable before surgery in most specialties and therefore beyond the scope of this chapter, as are micronutrient abnormalities and re-feeding syndrome.

Malnutrition can be further classified as (1) starvation-related (e.g., psychiatric feeding disorders, which will not be covered further in this chapter); (2) chronic disease-related malnutrition where the inflammation is chronic and mild-to-moderate in severity, such as slow growing gastrointestinal (GI) malignancies and inflammatory bowel disease (IBD); and (3) acute disease or injury-related malnutrition where the inflammation is acute and severe, such as intra-abdominal septic catastrophe [7, 8].

Malnutrition

Malnutrition (or undernutrition) is a state resulting from relative lack of intake or uptake of nutrition, typically protein calories, that leads to altered body composition and body cell mass, in turn leading to diminished physical and mental function and sub-optimal clinical outcome from disease [7].

In the context of surgical pathophysiology, disease causes malnutrition through two main mechanisms. Many diseases directly impair gastrointestinal function, through obstruction from mechanical stricturing of hollow viscera, disturbance of digestive mechanisms, inflammation of the gastrointestinal mucosa, and other mechanisms. Alternatively, accelerated tissue catabolism due to chronic systemic inflammation (e.g., cancer cachexia) causes malnutrition despite an unchanged nutritional intake and uptake.

In practice, many surgical diseases cause malnutrition through both these main processes. It is therefore important to

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consider both these etiologies when optimizing patients, so that both the delivery of nutrition and any sources of systemic inflammation are optimized to the greatest extent possible. For example, in advanced Crohn's disease, abscesses must be treated in parallel with nutritional support; otherwise abdominal sepsis will prevent positive net caloric and nitrogen balance [9].

Sarcopenia

Sarcopenia is defined as a progressive, generalized loss of skeletal muscle mass, strength, and function, with a consequent risk of adverse outcomes from disease [7]. It is caused by normal aging, muscular deconditioning and atrophy from restricted mobility, and dietary protein deficiency, but not necessarily decreased total caloric (carbohydrate and fat) intake. This condition is not detected by conventional malnutrition risk screening, but strictly requires both functional testing and cross-sectional imaging of defined muscular compartments.

Sarcopenia has recently emerged as an important nutritional disorder in surgical patients, as it has been independently associated with poor outcomes after major surgery [10, 11]. Importantly, sarcopenia may exist in patients who are not malnourished. In fact, sarcopenia is often present in people who are also obese (sarcopenic obesity, low skeletal muscle mass with excess adipose mass), and this condition may be a particular risk for poor outcomes from major surgery [12].

Current Assessment of Nutritional Disorders

Malnutrition Risk Screening

Current clinical guidance recommends that all hospitalized patients are screened for malnutrition on admission [13]. Contemporary screening tools are simple scoring systems based on body mass index (BMI), degree of recent weight loss, recent food intake, disease severity, and age. Screening tools that have been validated and shown to predict outcomes in clinical populations include Malnutrition Universal Screening Tool (MUST) (www.bapen.org.uk), Nutrition Risk Screening-2002 (NRS- 2002) [7], the Short Nutritional Assessment Questionnaire (SNAQ) [14], and the Subjective Global Assessment (SGA) [15].

There are several opportunities to screen elective surgical patients, such as at the time of listing for surgery, at preoperative anesthetic assessment, or on admission. For effective intervention, it is important that malnutrition screening is performed as early as possible in the patient's care pathway and ideally should be recognized and treated by the primary care provider team.

The MUST score is a representative example of a malnutrition risk screening tool. The health care professional assesses three simple variables: BMI, degree of weight loss, and whether acute disease is interfering with the ability to eat (Fig. 6.1). A score between 0 and 6 is then calculated and used to triage the patient to more complete nutritional assessment and intervention as appropriate.

A recent modification of the MUST score is the Peri-Operative Nutritional Score (Fig. 6.2). This modification, widely used in the United States, treats the variables of the MUST score as binary variables and adds hypoalbuminemia (serum albumin <3 g/dL) as a parameter. Thus a patient with either a low BMI, weight loss >10%, 50% reduction in oral intake, or low albumin is referred on to formal nutritional assessment and intervention.

Serum markers should not by themselves be used for malnutrition risk screening or nutritional assessment. Serum concentrations of transporter proteins such as albumin decrease quickly in inflammatory conditions, where acute phase protein synthesis is prioritized instead of transporter protein synthesis. Such changes are frequently observed in

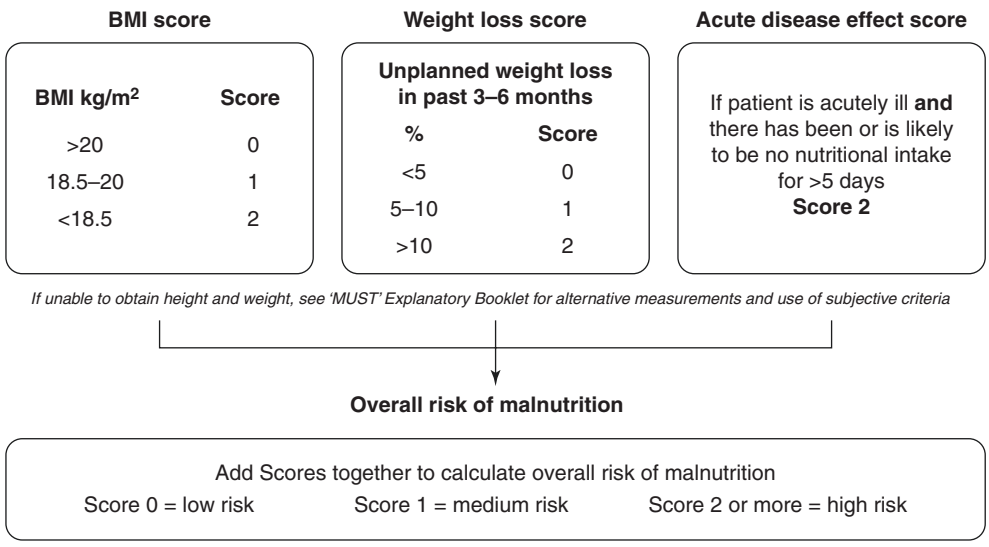

Fig. 6.1 The Malnutrition Universal Screening Tool (MUST). (© BAPEN: the British Association for Parenteral and Enteral Nutrition. The "Malnutrition Universal Screening Tool" ("MUST") is reproduced here with the kind permission of BAPEN (British Association for Parenteral and Enteral Nutrition). For further information on "MUST," see www.bapen.org.uk Copyright BAPEN 2012)

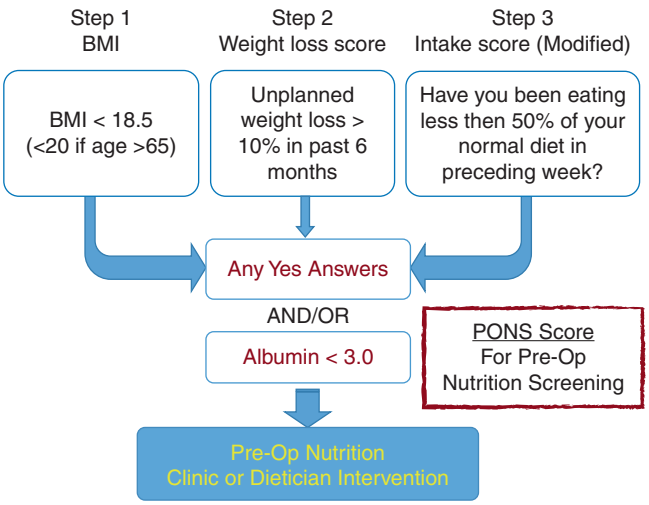

Fig. 6.2 Peri-Operative Nutritional Score (PONS).(Figure reused with the permission of the Perioperative Quality Initiative (POQI))

septic or cachectic surgical patients. Therefore, while a low serum concentration is often observed in surgical patients, this finding is an expression of systemic inflammation, rather than evidence of malnutrition. Importantly, this is clearly illustrated by studies showing normal serum albumin concentrations in conditions of severe and pure protein-calorie malnutrition [16].

Sarcopenia Screening

Sarcopenia is a risk factor particularly in older people, and is not detected by malnutrition risk screening tools. This common condition requires more complex assessment, as it is defined by both muscle volume and function. The European Working Group on Sarcopenia in Older Persons recommend screening for sarcopenia in all patients aged 65 years or older, specifically by measuring their gait speed and handgrip strength as a first step [17]. Patients with impaired muscle function on these two measures then undergo muscle mass assessment by bio-impedance analysis, dual energy X-ray absorptiometry, or anthropometry. Sarcopenia is diagnosed if muscle mass is significantly less than age- and sex-matched control subjects [17].

Exploratory work utilizing preoperative computer tomography (CT) scans obtained for clinical purposes to also estimate lean tissue mass have been published [10, 11, 18]. Although such methodology does not include a functional component, as would be recommended by the European Working Group on Sarcopenia in Older Persons, sarcopenia diagnosed by this methodology has been independently associated with clinical outcomes. In surgical patients, therefore, it may be reasonable to consider CT an appropriate alternative for sarcopenia screening, and this warrants further evaluation.

Epidemiology of Nutritional Disorders in Surgical Patients

Studies based on malnutrition risk screening in patients scheduled for surgery have consistently highlighted a significant prevalence of malnutrition in several surgical specialties. Contemporary, detailed studies report similar rates in esophagogastric surgery (20–26%) [2, 19] and colorectal surgery (20–27%) [3, 20], whereas somewhat lower rates have been reported in elective orthopedic surgery (15%) [21].

The prevalence and significance of sarcopenia in the surgical population has only recently been investigated. Nearly all such studies have defined sarcopenia as a truncal muscle area at the third lumbar level on preoperative CT imaging below a chosen cutoff value. Using this method, no less than 39–48% of patients undergoing colorectal surgery have been found to be sarcopenic [10, 18]. Interestingly, mean body mass index among sarcopenic patients in one study was 26.1 kg/m^2, further emphasizing the point that sarcopenia is a separate nutrition disorder from malnutrition [10].

A small number of studies have used the European Working Group on Sarcopenia in Older Persons definition, requiring both reduced muscle mass and impaired measured muscle function for a diagnosis of sarcopenia, and in those studies the prevalence has been considerably lower at 12–21% [22–24].

Clinical Significance of Nutritional Disorders in Surgical Patients

Malnutrition

The first study linking malnutrition and poor postoperative outcome is the 1936 landmark study by Studley et al., which reported a direct association between magnitude of preoperative weight loss and the risk of death after gastric ulcer surgery [1]. Contemporary studies using multivariable regression methodology have confirmed that preoperative malnutrition is an independent predictor for increased mortality, length of hospital stay, and costs [25], as well as infectious complications and anastomotic dehiscence [26].

Sarcopenia

Many published studies based on cross-sectional imaging have found associations between sarcopenia and adverse postoperative outcomes. In colorectal surgery, sarcopenia has been independently associated with increased risks of postoperative infection, length of stay, and mortality risk [10, 18]. The associations between sarcopenia and poor postoperative outcomes is predominantly seen in people aged

>65 years [10]. Recent meta-analysis in upper and lower gastrointestinal cancer surgery found a 30% increase in major complication rates, and a 40% increase in total morbidity, in sarcopenic patients [27]. Importantly, this pooled analysis also found that sarcopenia frequently was a strong independent risk factor for postoperative morbidity on multivariable analysis [27].

Similar to sarcopenia, sarcopenic obesity, a condition of both low muscle mass and excess adipose mass, has recently garnered much attention [28]. It is sometimes referred to as "silent sarcopenia" as the low skeletal muscle mass is hidden under the excess adipose. The association of sarcopenic obesity with sub-optimal postoperative outcomes has been studied in a variety of abdominopelvic disease states—mostly gastrointestinal malignancies. Sarcopenic obesity is generally diagnosed via cross-sectional imaging with automated segmentation of key intra-abdominal muscular (psoas muscle) and visceral fat compartments. Although difficult to diagnose, and a marker of poor outcomes, in cancer patients especially, it is difficult to treat preoperatively in a short period of time. Recommendations focus not only on increasing physical activity (physiotherapy) and protein intake but also limiting dietary fat and carbohydrate intake.

Nutritional Intervention in the Preoperative Patient

If surgery can be delayed by several weeks, referral to a dietitian for formal nutritional assessment, nutritional intervention, and monitoring of changes can be considered. The specific minimal protein requirement for nonstressed adult patients includes 1.2–2 grams of protein/kg/day, translating to 84–140 grams of protein per day for a 70 kg adult.

However, in many situations the surgical team has to initiate nutritional support immediately in the patient found to be at risk of malnutrition at screening, as surgery cannot be delayed for clinical reasons. It is therefore important that surgeons formulate strategies for nutritional support in the most common clinical scenarios that they encounter (Table 6.1). Common such scenarios may be characterized by different timings of surgery and different safety and effectiveness of oral or enteral nutritional support in different disease states.

The strongest evidence for preoperative nutritional intervention in malnourished patients comes from a 1997 meta-analysis of a range of randomized trials of parenteral nutrition given during 5–23 days prior to major surgery [29]. This relatively brief period of nutritional support resulted in a 25% relative reduction of overall complication rates after surgery on pooled analysis [29]. The period of nutritional support was too brief to allow for restoration, or even significant increase, of lean tissue mass. These data therefore support a pragmatic goal of preoperative nutritional support of reversing weight loss to achieve a modest weight gain, rather than aiming for full restoration of premorbid or ideal body weight.

Table 6.1 Summary of key messages

Definitions	Malnutrition – a state resulting from relative lack of intake or uptake of nutrition, typically protein calories, that leads to altered body composition and body cell mass, in turn leading to diminished physical and mental function and sub-optimal clinical outcome from disease Sarcopenia – a progressive, generalized loss of skeletal muscle mass, strength, and function, with a consequent risk of adverse outcomes from disease Sarcopenic obesity – a disease state manifesting as both low muscle and abnormally high body mass index; hidden malnutrition
Malnutrition screening	Malnutrition Universal Screening Tool (MUST, Fig. 6.1) Peri-Operative Nutritional Score (PONS, Fig. 6.2)
Surgical epidemiology	Nutritional disorders are very common, as a significant minority of gastrointestinal surgical patients, at least 25%, have nutritional disorders at the time of surgical referral. Recognizing nutritional disorders is the first step in treatment
Nutritional intervention	Although a balanced diet is essential to good health, perioperative nutritional interventions should focus on a high-protein diet, with 1.2–2 grams of protein/kg/day. Mode of administration is optimally enteral, with parental nutrition reserved for those who cannot meet requirements through enteral nutrition. The aim is not full restoration of premorbid or ideal body weight, but halting of weight loss with modest weight gain
Immunonutrition	Current data and clinical recommendations do not support routine use of preoperative immunonutrition
Vitamin supplements	Goal to optimize collagen synthesis, especially in the setting of chronic steroid use
Exclusive enteral nutrition	A mono-diet using a polymeric oral or enteral diet that has been shown to be associated with anti-inflammatory effects in the short-term and may prevent disease flare in patients with Crohn's disease weaned from disease-modifying medications before surgery

Parenteral nutrition typically requires at least day-admission to hospital and is associated with well-defined risks related to access (e.g., line sepsis, deep vein thrombosis) and metabolic tolerance (e.g., increased liver function tests, insulin resistance). For these reasons, preoperative parenteral nutritional support should be reserved for patients with a contraindication for oral diet or oral nutritional support, not uncommon in gastrointestinal and colorectal surgical diseases. Examples include disease associated with an obstruction in the gastrointestinal tract: gastric outlet obstruction with inability to access midgut, obstructing gastrointestinal malignancy, obstructing diverticular disease, or Crohn's

disease. Another example is penetrating rather than stricturing Crohn's disease, where oral diet may exacerbate phlegmons and abscesses.

For most patients with preoperative malnutrition, effective oral diet and nutritional support is feasible. However, the evidence that preoperative oral nutritional support improves outcomes in malnourished surgical patients is limited. A recent assessor-blinded randomized trial demonstrated that, among weight-losing patients with colorectal cancer, administration of an oral nutritional supplement for a median of 8 days was associated with a reduced perioperative weight loss and a reduced incidence of infectious complications [30].

Few data are available on the efficacy of interventions to improve preoperative sarcopenia. Based on a substantial literature in sports physiology, nutritional support in combination with endurance and resistance exercise should be helpful in building muscle mass in both young and elderly people [31]. However, such intervention programs often stretch over a period of months. It is not clear what benefits can be seen with shorter intervention programs, which would be required for many surgical patients with sarcopenia.

The concept of prehabilitation—combining nutritional support and endurance and resistance exercise during a shorter time period before surgery—has recently been investigated. Some positive results have been shown, such as improved 6-minute walking distances after a prehabilitation program lasting a median of 24 days, when compared to controls [32]. This randomized trial was undertaken in consecutive patients regardless of nutritional state. In a further randomized trial undertaken specifically in high-risk patients, an intensive 4-week prehabilitation program was found to result in improved exercise endurance as well as less postoperative complications [33].

Obesity

It is well established that BMI is directly correlated to adverse postoperative outcomes. Many would argue that preoperative weight loss is difficult to achieve; however, for some elective operations, emerging evidence suggests that preoperative diets may positively influence postoperative outcomes. Specifically, several studies have shown that a 1-week low-calorie, low-fat diet was associated with decreased hepatic steatosis and with a concomitant decrease in intra- and postoperative bleeding [34, 35]. A short-term calorie and protein-restricted diet has recently been shown to also be feasible in kidney donors and recipients [36].

From a pragmatic perspective, obese patients awaiting elective surgery may be counseled regarding lifestyle modification with increased water intake, restricting carbohydrate intake, and elimination of carbohydrate-rich foods that lack nutritional value (sugary, corn syrup-based drinks, alcoholic beverages, cakes, and sweets). Note that weight loss is considered by many to be a prerequisite for elective incisional ventral hernia repair, and these patients may benefit from referral for cognitive behavioral therapy for weight loss and approach with proven efficacy prior to bariatric surgery [37].

Immunonutrition

Major surgery is associated with derangements in many micronutrients required to maintain immunocompetence. These micronutrients include specific amino acids (e.g., glutamine and arginine), polyunsaturated fatty acids (omega-3 fatty acids), nucleotides, and RNA. So-called immunonutrition has therefore been developed, providing a range of such micronutrients in addition to the usual macronutrients.

Many trials have evaluated orally administered immunonutrition in the lead-up to surgery, in both well-nourished and malnourished subjects. Recent meta-analyses have demonstrated that most trials of immunonutrition products, although many show promising results, suffer from significant bias [38, 39]. Specifically, most were funded by industry, and this bias is often insufficiently disclosed [38, 39]. Most importantly, it has been demonstrated that industry funding of trials in surgery greatly influence findings. In immunonutrition, industry-funded trials were found to be manyfold more likely to report positive outcomes from the intervention evaluated (odds ratio 7.8) [38]. When only trials at low risk of such bias are included in meta-analysis, no beneficial effects on mortality, overall complications, or infectious complications are seen from immunonutrition [39].

Currently available clinical guidelines from ESPEN and the ERAS Society have not universally included recommendations to routinely use immunonutrition [40, 41]. However, recent data has modified this situation for some gastrointestinal surgery [42–44].

Therefore, while there is a case for provision of calories, proteins, and some micronutrients in malnourished patients for a period leading up to major surgery, orally or enterally when possible, there is currently no established role for preoperative immunonutrition.

Vitamin Supplementation

Although vitamin supplementation is a routine aspect of parenteral nutritional support, one aspect of perioperative nutritional supplementation that has received little attention is enteral perioperative vitamin supplementation. Such short-term interventions are generally low cost and safe (if not taken in excess quantities).

Although a well-balanced healthy diet provides most individuals with the recommended daily requirements, surgical patients are often in an abnormal health state and thus may reasonably be expected to have higher than typical vitamin requirements. Although there is no proven benefit to long-term daily vitamin supplementation, from a risk-benefit perspective, empiric short-term daily vitamin use before and after surgery would reasonably be expected to be no risk-low benefit, thus favoring its implementation. Specific vitamin supplementation for anemic patients include adequate levels of folate, ascorbic acid, and enteral iron. Vitamin supplements that optimize collagen synthesis include ascorbic acid and zinc sulfate, as well as high-dose retinoic acid (vitamin A) for steroid-dependent patients, the former which was demonstrated to be efficacious in animal models [45–47].

Finally, certain individuals are prone to significant, chronic vitamin deficiencies, such as vitamin D deficiency after bariatric surgery, B12 deficiency after terminal ileal resection, and others.

Example of Disease-Specific Considerations

Crohn's Disease

Patients with Crohn's disease represent a particular subgroup of nutritionally at-risk patients who often have bowel damage severe enough to warrant total parenteral nutrition. This is often the case due to the severity of the malnutrition and that enteric nutritional intake may be limited by it aggravating abdominal pain.

However, data (mostly from pediatric literature) has demonstrated that exclusive enteral nutrition (EEN), which is essentially a polymeric diet using a single high-protein oral nutritional supplement, may be useful in this patient population. Specifically, due to complex interactions of a diet of normal foodstuffs with the intestinal microbiome and physiologic gut burden, EEN in Crohn's disease has been shown to be a disease-modifying therapy in Crohn's disease in and of itself. In fact, switching a patient to EEN may reduce abdominal pain and can have anti-inflammatory effects, allowing steroid weaning as a bridge to surgery.

People with Crohn's disease are at particular risk of malnutrition, due to a combination of factors including decreased oral intake, malabsorption due to mucosal disease, and catabolism due to systemic inflammation. A large proportion of patients requiring surgery are malnourished. In addition to the risks of added postoperative morbidity associated with malnutrition, reviewed above, in surgery for Crohn's disease, there are specific risks described that relate to anastomotic complications. Several studies have identified preoperative weight loss in the 5–10% range as an independent predictor of intra-abdominal septic complications [48–50]. Treating malnutrition is therefore particularly important in this population of patients. Preoperative optimization programs have emerged for Crohn's disease, incorporating a period of preoperative nutritional support in the form of either polymeric diet or parenteral nutrition, and preliminary data suggest improved outcomes [50–53]. In one meta-analysis, the number needed to treat was 2 for intervention with oral or enteral nutrition before surgery for Crohn's disease in malnourished patients [53]. There is also some evidence that perioperative enteral nutrition with elemental self-intubation was associated with a lower 5-year recurrence of Crohn's disease [54].

Conclusions and Future Directions

Patients undergoing major surgery in the setting of enhanced recovery should routinely be screened preoperatively for malnutrition using one of several readily available bedside tools. Those identified with nutritional disorders require referral to a nutritionist for consideration of intervention as the underlying surgical pathology and times allows. Patients undergoing gastrointestinal and oncologic surgery represent several at-risk groups as their pathology may directly contribute to nutritional disorders. In the twenty-first century, the old adage of "if the gut works, use it" still holds true. Exclusive enteral nutrition may have an increasing role in affecting both short- and long-term perioperative outcomes, similar to how ERAS may be associated with improved long-term oncologic outcomes. In the near future, further developments in the area of food and nutrition science can reasonably be expected to further attenuate the association of nutritional disorders with sub-optimal postoperative outcomes.

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Anemia and Blood Management

7

Michael J. Scott

Introduction

This chapter discusses the Enhanced Recovery After Surgery (ERAS) principles of maintaining an optimal hemoglobin level to avoid the risk of perioperative organ dysfunction or red cell transfusion. It covers elective surgical cases and is not an exhaustive review of blood management. Preoperative treatment of anemia and minimizing the use of blood transfusion are two key strategies to reduce complications after surgery.

Anemia: Incidence and Causes

Anemia is one of the commonest modifiable risk factors for patients undergoing major surgery. The World Health Organization (WHO) definition of anemia is a hemoglobin (Hb) level of <13.0 g/dL for men and <12 g/dL for women. This is based on large population studies as normal. However, a proportion of women are iron deficient due to blood loss during menses with one study showing around 25% of those with an Hb of 12 g/dL may be iron deficient [1]. Therefore a large proportion of women are entering surgery either with a low Hb level or with iron deficiency or both. This means that their ability to respond to blood loss is impaired, and this can lead to delayed return to normal functional activity and the feeling of tiredness. Women also have a lower circulating blood volume and red cell mass. Volumes of surgical blood loss are surprisingly consistent between standardized operations such as hip replacement despite differences in the size of patients [2]. Therefore a woman can lose a similar volume of blood to a man in surgery, but the impact on their drop in Hb is higher due to their lower starting red cell mass and circulatory blood volume. Another example is women are much more likely to be transfused in cardiac surgery than men because of the necessary priming volume for cardiac bypass circuits.

Consensus guidelines on perioperative anemia agree that all patients should be screened for anemia prior to major surgery. Rationalizing laboratory tests at the time of testing can be important for cost savings. There are now noninvasive oximeters measuring Hb that are the same size as pulse oximeters and can be used as a quick noninvasive screening process. This can help the logistics of ordering follow-up laboratory studies, which are necessary to categorize the type of anemia if the oximeter value shows anemia. Then iron studies can be drawn at the same time as the initial full blood count.

Patients presenting for surgery may have many factors as a cause for anemia: acute or chronic blood loss, vitamin B12 or folate deficiency, or anemia of chronic disease. There may also be a combination of these, and they may be related or unrelated to their reason for surgery [3]. Chemotherapy can also induce anemia due to toxicity of the bone marrow. Anemia should be investigated appropriately prior to correction, particularly if it does not fit with the clinical presentation for the reason for surgery. Most causes of anemia in patients undergoing major surgery is iron deficiency due to either blood loss due to the pathology (e.g., colon cancer) or anemia of chronic disease. The preoperative clinic should have standardized guidelines for referral of patients to the hospital internist, hematologist, or gastroenterologist when the cause of anemia is not obvious. Chronic renal failure is another cause for a low Hb, although these patients usually receive erythropoietin and iron infusions from their nephrologist.

Figure 7.1 shows how anemia can be screened and categorized [2]. Ferritin is a useful test for iron deficiency but can be raised in chronic inflammation. Therefore it is important to get iron studies so that the transferrin saturation (TSAT) is calculated. A TSAT less than 20% will confirm the diagnosis of iron deficiency.

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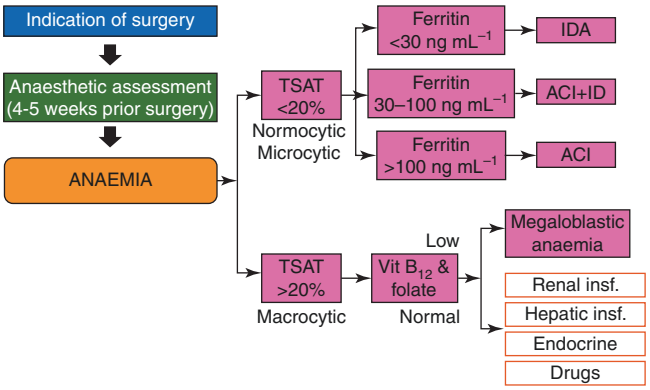

Fig. 7.1 Screening for anemia with appropriate blood tests. (Reprinted with permission from Muñoz et al. [2])

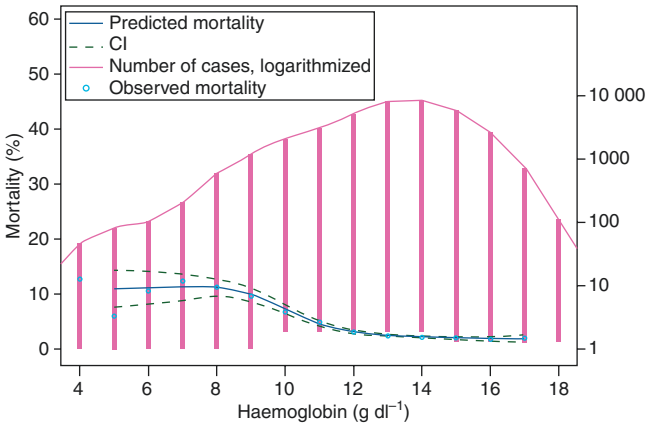

Fig. 7.2 Graph showing mortality risk with preoperative hemoglobin levels. (Reprinted with permission from Baron et al. [4])

Anemia of Chronic Disease

In anemia of chronic disease, such as inflammatory arthropathy or bowel disease, the iron regulatory protein hepcidin is activated in response to inflammation. This has many effects on iron metabolism including inhibiting recycling of iron from the breakdown of red blood cells, mobilization of iron to the marrow for hemopoiesis, and absorption of iron from the gastrointestinal (GI) tract. This reduces availability of iron stores for red cell production. The use of oral iron in these circumstances is therefore not very effective. Intravenous iron infusions can overcome this issue in many instances [3].

Anemia: Risks of Complications and Mortality

Anemia is a risk factor for all complications and mortality for patients undergoing major surgery [4, 5]. Anemia is surprisingly common in patients presenting for surgery. Large data reported from Europe by the European Surgical Outcomes Study (EuSOS) group in all surgical specialties showed a prevalence of 31.1% of men and 26.5% of women [4]. There was an inflection for mortality with an Hb below 10.5 g/dl and an increased risk of complications, length of hospital stay, and use of intensive care resources the lower the Hb was at presentation prior to surgery (Fig. 7.2) [4].

The administration of blood products both pre- and perioperatively to correct anemia is also a causative factor for complications and impacts long-term survival in patients with cancer. Blood transfusion is therefore not an optimal treatment for anemia, and a restrictive blood transfusion policy should be adopted in surgery.

In one recent consensus document, the authors looked at 35 cohort studies [6]. They then performed a meta-analysis to identify the pooled odds ratio (OR) for adverse events in cardiac and non-cardiac surgery. This showed an association between preoperative anemia and:

1. In-hospital mortality (pooled OR, 2.09 [95% CI, 1.48–2.95])
2. 30-day mortality (pooled OR, 2.20 [95% CI, 1.68–2.88])
3. Acute myocardial infarction (AMI) (pooled OR, 1.39 [95%CI, 0.99–1.96])
4. Acute ischemic stroke or central nervous system complications (pooled OR, 1.19 [95% CI, 1.02–1.39]
5. Acute kidney injury, renal failure/dysfunction, or urinary complications (pooled OR, 1.78 [95% CI, 1.35–2.34])

A retrospective series of 23 388 patients undergoing colorectal surgery showed that 7.9% of patients received blood transfusions during their hospital admission. There was an increase in organ space surgical site infections (SSI) (OR 2.93) and septic shock (OR 9.23). In one series of elective orthopedic surgery for hip and knee replacement, a transfusion of blood products increased 4-year mortality by 10% [5]. In other studies looking at patients with cancer metastasis to the liver undergoing liver resection, the transfusion of blood products is a risk for poor short- and long-term outcomes [7, 8].

It is therefore essential to optimize a patient's hemoglobin levels prior to surgery. The time window to do this will vary according to the reason and urgency for surgery and how rapidly blood loss is occurring.

Optimal Perioperative Hemoglobin Targets

The American Society of Anesthesiologists (ASA) and European Society of Anaesthesiology (ESA) recommend that a minimum Hb level of 7.0–10.0 is maintained through the perioperative period. The ASA recommends maintaining a minimum Hb target of 6.0–10.0 g/dl according to the type of surgery and comorbidities of the patient [9].

However, this does not mean these levels are ideal. As blood loss is not always predictable for surgery, a patient's preoperative Hb should be targeted such that the Hb prior to

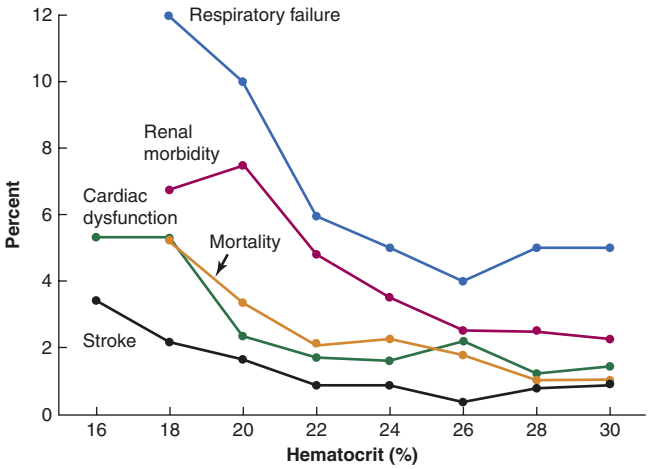

Fig. 7.3 Graph showing risk of mortality and organ dysfunction with different comorbidities in cardiac surgery. (Reprinted with permission from Loor et al. [10])

Table 7.1 Common procedures where there is a high chance of >500 ml blood loss or >10% of blood volume

Hip and knee arthroplasty
Spinal surgery – fusion >1 level
Cardiac surgery
Thoracic surgery
Major hepatobiliary surgery/liver resection surgery
Colorectal bowel resection
Esophagectomy and gastric resection surgery
Pancreatic surgery
Cystectomy
Transplant surgery – liver, lung, heart

surgery is at a level that with the predicted average blood loss the nadir hematocrit is not reached. Nadir hematocrit is the level of Hb below which there is likely to be complications due to a failure of oxygen delivery to organs. A composite risk graph was developed for cardiac patients by Loor et al. (Fig. 7.3) [10]. This shows that patients with different comorbidities have a different nadir Hb below which mortality rises.

Therefore for elective surgery a target Hb of >12–13 g/dl should be set. For patients undergoing urgent surgery, Hb should be optimized as much as possible prior to surgery (Table 7.1).

Preoperative Interventions to Increase Hemoglobin in Iron Deficiency Anemia

Oral Iron Therapy

Oral iron is a simple and cheap way of correcting iron deficiency anemia but may be poorly tolerated due to gastrointestinal side effects. The absorption is reduced when patients are on a proton pump inhibitor for gastroesophageal reflux due to the poor conversion of the iron by acid into an absorbable form. The absorption of iron may be better by using lower doses than the standard 200 mg such as 40–60 mg per day or alternating slightly higher doses of 80–100 mg [3]. However, the response and correction of anemia with oral iron may be slow, particularly if there is ongoing blood loss. Intravenous iron infusion may be worth considering to give a kick start in this group or in nonresponders (Table 7.2).

Table 7.2 Anemia Key Points

All patients undergoing major surgery should be screened for anemia
Anemia is a modifiable risk factor for mortality and complications and should be investigated and treated appropriately prior to surgery
The degree of anemia correction possible before surgery may depend on the urgency of surgery and whether the ongoing blood loss is faster than the patient can make up with hematopoiesis
Iron deficiency is common, particularly in women even with normal Hb levels
Iron studies comprising Ferritin, Fe, TIBC and TSAT folate, and B12 deficiency should be performed as soon as anemia is detected to allow maximal time for correction prior to surgery. Other causes should also be tested for
Noninvasive Hb measurement can be a useful screening tool to trigger iron studies sooner, allowing more time for correction prior to surgery
Blood transfusion has its own associated risks and is not the treatment for a chronic problem at the time of surgery
All hospitals should have a patient blood management program
Unless there is known cause for the anemia, appropriate investigation should be performed prior to surgery (e.g., upper and lower GI endoscopy)
Proton pump inhibitors are a common cause of iron deficiency
Oral iron can be tried, but response is often slow and poorly tolerated
Anemia of chronic disease is a state of functional iron deficiency and may respond to intravenous iron
IV iron now comes in many sugar solutions that have a low anaphylaxis rate. However, immediate nanoparticle reaction is common but can be treated with steroids and antihistamines and temporarily stopping the infusion
Iron infusions should be considered in the following groups even without overt anemia: Women with expected blood loss, patients with chronic heart failure
Short-acting ESAs should be used with caution until further evidence emerges but may benefit patients with resistant anemia

Intravenous Iron Infusions

Although older iron infusions had a significant number of serious adverse effects, there are several newer sugar-based iron infusions available in clinical practice with a low serious adverse reaction rate of between 7 and 38 per million [11]. Acute reactions comprising itching, vasodilation, and transient hypotension are normally mediated via complement activation due to nanoparticles rather than a classic immunoglobulin E (IgE)-mediated immune response [12]. By pausing the infusion and giving intravenous steroids and antihistamines, this can be rectified and the infusion continued more slowly. Timing and number of infusions depend on the urgency of surgery. There are many online calculators to

work out the iron deficit for a patient's size and current Hb, although these do not take into account active blood loss. Administering 1–1.5 g usually restores iron levels back to normal. This should be given in divided doses such as iron sucrose 300 mg every 1–2 weeks, although iron carboxymellose may be given in doses of 1 g in a single sitting. Reticulocytosis occurs at 3–5 days. In one study the single 1 g dose increased Hb by 0.8 g/dl over 8 days [13].

A recent meta-analysis of the use of intravenous iron in the preoperative and postoperative phases demonstrated efficacy in raising Hb levels, reduced red blood cell use, and improved patient well-being [14]. Iron infusions have also been used to correct anemia to improve cardiac function in chronic heart failure, where the incidence of anemia is common [15]. This may be an important intervention to decrease this group's perioperative risk.

Use of Erythropoietin-Stimulating Agents (ESA)

The addition of an erythropoietin-stimulating agent (ESA) is not usually needed to treat preoperative anemia; however, there are some cases of resistant anemia where their use may be of benefit. A recent meta-analysis of 32 studies showed that short-acting ESAs can be safely used preoperatively to increase Hb levels if dosed appropriately [16]. There was significant reduction in allogenic red cell transfusion during the perioperative period. The main risks previously reported were increased venous thromboembolism (VTE) and possible cancer effects. However, in this meta-analysis, the risk of VTE was not demonstrated. During ESA treatment, hemoglobin may be increased to the lowest concentration needed to avoid transfusions. Timing of infusions and effectiveness in different surgical populations has still to be determined by large-scale studies. Iron replacement may be used to improve hemoglobin response and reduce red blood cell (RBC) transfusions for patients receiving ESA with or without iron deficiency.

In a recent international consensus guide by Mueller et al., in order to reduce the need for RBC transfusions, the following recommendations for ESAs can be offered to patients who have chemotherapy-associated anemia [6]:

- *Recommendation 1.1* – Depending on clinical circumstances, ESAs may be offered to patients with chemotherapy-associated anemia whose cancer treatment is not curative in intent and whose hemoglobin has declined to <10 g/dL. RBC transfusion is also an option, depending on the severity of the anemia or clinical circumstances (type, evidence based; evidence quality, high; strength of recommendation, strong).
- *Recommendation 1.2* – ESAs should not be offered to patients with chemotherapy-associated anemia whose cancer treatment is curative in intent (type, evidence based; evidence quality, intermediate; strength of recommendation, strong).

Perioperative Blood Management

The blood has several components including red bloods cells, white blood cells, platelets, and plasma containing clotting factors and fibrinogen. This chapter is focused on the management of reducing red blood cell transfusion.

All patients should have a restrictive blood transfusion plan. As stated earlier in the chapter, current guidelines are to maintain an Hb of 7.0–10.0 g/dl according to the type of surgery and the comorbidities of the patient.

Reducing Blood Loss During Surgery and the Postoperative Period

Surgical and Anesthetic Technique to Reduce Blood Loss

Blood loss is due to direct trauma of tissues or escape of blood from veins or arteries. The surgeon, type of surgery, and surgical technique are therefore key determinants of blood loss. Optimal dissection technique and the use of modern high-energy instruments such as harmonic scalpel can reduce bleeding during dissection. Rapid control of sources of bleeding is also important. In some high-risk blood loss procedures, such as liver surgery, certain techniques are well established such as the Pringle maneuver. Anesthetic technique using agents to lower the venous pressure and control arterial pressure and stroke volume can also be useful to reduce the amount of blood loss. Appropriate hemodynamic monitoring is mandatory during these surgeries.

Red Cell Salvage

The use of red cell salvage is useful where there is an expected high blood loss. Red cells are scavenged during suction and washed and recycled to be reinfused. There is a high cost of setup of these machines, but more recently there are more cost-effective solutions so they can be used in lower blood loss situations. As the cost of blood is increasing, red cell salvage is becoming a more cost-effective intervention. The use in cancer surgery has been strongly debated because of the principle of reintroducing cancer cells into the circulation. However, these cells were there in the first place, and the avoidance of red cell transfusion is important for oncological outcomes.

Antifibrinolytics

The use of antifibrinolytics, such as tranexamic acid and aminocaproic acid, is gaining popularity in many surgical specialties. The mode of action is to inhibit plasminogen and the formation of plasmin, which can reduce clot stability. They can be given systemically or used topically. Usually these are given prior to the start of surgery and redosed; 1 g of tranexamic acid appears to give optimal benefit with redosing occuring every 6 hours as necessary. Higher doses raise the risk of seizures. In a meta-analysis antifibrinolytics have been shown to be effective in reducing surgical bleeding in many different surgical specialties [17]. Despite initial concerns the risk of venous thromboembolism does not seem to be significantly higher than control. The CRASH2 study in trauma showed it is important that tranexamic acid be used early in the injury process [18].

Reducing Frequency and Volume of Blood Tests

The simple steps of reducing the number of blood tests after surgery and using smaller collecting tubes can have a dramatic decrease in the amount of blood taken out of the patient.

Conclusion

Anemia is common in patients presenting for major surgery and increases all-cause morbidity. All patients should be screened for anemia and the cause identified. Correction prior to surgery can be achieved in many patients, particularly those patients with iron deficiency because modern intravenous iron preparations are safe and can be given as an outpatient basis. Erythropoietin-Stimulating Agents should be used with caution. The degree of correction may be limited depending on the urgency of surgery. Blood transfusion has long-term effects and should be avoided if possible preoperatively.

All hospitals should offer a blood management strategy to minimize individual blood transfusion.

Intraoperative and postoperative strategies can reduce the amount of blood loss. Surgical technique is key, together with the approach (open or laparoscopic/robotic). Tranexamic acid and intraoperative cell salvage are proven techniques to reduce blood transfusion. In the postoperative period, reducing frequency and volume of blood tests can also reduce the amount of blood loss.

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Perioperative Smoking and Alcohol Cessation

8

Gabriele Baldini

Smoking Cessation

The proportion of adults who are smoking in the developed world is decreasing (one out of five adults smoke) [1]. According to the US Centers for Disease Control and Prevention (CDC), the proportion of adults smoking cigarettes in the United States decreased from 23.3% (46.5 million) in 2000 to 15.5% (37.8 millions) in 2016 [2].

Frequently, preoperative interventions aim at optimizing a patient's comorbidities, while minimal efforts are made to modify lifestyle habits that also have been shown to increase postoperative morbidity. Despite it is well proven that smoking cessation is highly feasible, readily available, and a cost-effective intervention, interventions to help surgical patients quit smoking before surgery are rarely provided as routine surgical care.

Interestingly, perioperative physicians systematically inquire about lifestyle habits such as smoking, but this information is primarily used to stratify perioperative risks rather than triggering behavioral and lifestyle changes.

Current evidence demonstrates that preoperative smoking is associated with increased morbidity and mortality [3]. Considering that smoking is a potentially modifiable preoperative risk factor, interventions that aim at helping patients quit smoking before surgery should be more frequently adopted. Perioperative physicians and caregivers should take advantage of the perioperative period and encourage and support patients to achieve short- and long-term smoking cessation.

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Why, When, Who, and How?

Smoking: Perioperative Pathophysiologic Changes

Airway and Respiratory System Smoking has been shown to induce inflammatory changes and impair the respiratory immune function. These effects are particularly important in patients receiving general anesthesia during which some of the physiologic mechanisms protecting the respiratory system—such as bronchial mucus transport, macrophage function, and microbicidal cellular activity—are negatively affected by smoking [4].

Smoking causes an alteration of the airway epithelial function and mucus production (increased volume and composition) and decreases mucociliary clearance [4, 5]. Clinically, these pathophysiologic changes can determine an increased irritability of the airway that is associated with intraoperative cough, laryngospasm, and breath holding [4]. With time, hyperplasia of muscle fibers and fibrosis caused by smoking determine a more rapid decline in forced expiratory volume in 1 second compared to non-smokers [4].

Cardiovascular System It is well recognized that smoking is a risk factor for atherosclerosis, coronary artery disease, heart failure, and peripheral vascular diseases. This is mainly due to nicotine, but also to many other constituents of cigarette smoke. Nicotine directly and indirectly, by stimulating the sympathetic system, increases myocardial work by increasing heart rate, blood pressure, and contractility. Smoking causes coronary vasoconstriction in patients with coronary artery disease, and it induces a hypercoagulable and chronic inflammatory state [4].

Carbon monoxide (CO) released by smoking tobacco decreases the amount of oxygen bound to the hemoglobin and decreases oxygen release to tissue. These effects predispose to angina and ventricular arrhythmia. Moreover, CO and cyanide, also released in cigarette smoke, impair mito-

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chondrial respiration by inhibiting enzymes such as the cytochrome c oxidase.

Considering that the half-lives of nicotine and carboxyhemoglobin are very short (1 and 4 hours, respectively), it is plausible to expect that cardiovascular benefits could be observed even for a brief period of smoking cessation. This is supported by evidence demonstrating that carbon monoxide levels correlate with ischemic electrocardiographic signs in anesthetized surgical patients. Improvement of smoking-related diseases, such as atherosclerosis, coronary disease, and peripheral vascular disease, may occur more slowly [4].

Wound and Bone Healing Many studies have reported that smokers have a higher risk to develop postoperative wound healing complications, such as dehiscence and infection. Decreased tissue oxygenation caused by nicotine-induced vasoconstriction and by carboxyhemoglobin, together with many other risk factors, contributes to development of these complications. However, experimental studies using high-nicotine concentrations (far above the levels measured in active smokers) have also suggested that smoking impairs the tissue and immune response to injury, thus compromising wound healing. Paradoxically, topical application of nicotine to wounds has shown to promote angiogenesis and accelerate healing [6]. These findings suggest that other substances than nicotine produced by cigarette smoke might also affect wound healing. The effect of nicotine on wound healing probably depends on many other factors, such as dose, route of administration, acute vs. chronic exposure, and modulation of neuro-inflammatory mechanisms involved in the response to tissue injury [4]. Moreover, impaired nitric oxide release—frequently present in patients with microvascular diseases such as smokers—might further delay wound healing [4].

Similarly, smoking has been shown to impair bone healing and increase the risk of non-union especially after major spine surgery. These risks are higher if smoking is continued in the postoperative period. Several mechanisms have been proposed [4]. Experimental studies have shown that nicotine at relatively high dose negatively affects bone healing by inhibiting several cellular pathways. In particular inhibition of tumor necrosis factor-alpha (TNF-α) secretion through the activation of the cholinergic anti-inflammatory pathway seems to play a major role [7].

Nervous System Function Nicotine binds to the ion channel nicotine acetylcholine receptors (nAChRs) widespread in the central and peripheral nervous system. Nicotine acetylcholine receptors are also located in the autonomic ganglia, the adrenal glands, and at neuromuscular junctions. Several subtypes of nAChRs have been identified, depending on their subtype units. Nicotine acts mostly as a receptor agonist, but when it binds certain nAChR subunits, it antagonizes the effect of acetylcholine. Because of the ubiquity of nAChRs, activation of these receptors produces different effects, depending on the anatomical location and type of subunits activated. In the central nervous system (CNS), activation of nAChRs modulates the release of several neurotransmitters that influence several CNS functions. As a result, the effect of nicotine on the CNS function is not completely understood and is complex in nature. Nicotine can produce psychotropic effects, such as reward and pleasure, by activating the dopaminergic system, but it can also cause unpleasant effects, such as anxiety and agitation, especially in nicotine-naïve patients.

Experimental and clinical studies also demonstrate that nicotine affects nociception, but the effects are complex and inconsistent. Animal studies show that systemic nicotine produces a mild analgesic effect when it stimulates nAChRs located in the CNS, while it increases pain perception when it stimulates nAChRs of peripheral nerves. Clinically, most of the studies have demonstrated that smoking increases pain threshold and tolerance, but other studies performed in smokers undergoing coronary artery bypass graft, oral surgery, and pelvic surgery have shown an increase of postoperative opioid requirements [4]. Although baseline and postoperative pain thresholds might be lower in smokers than in non-smokers, postoperative increase of pain score does not differ [8]. Evidence that nicotine affects perioperative pain perception comes also from the reported effects of abstinence and nicotine replacement therapy on pain thresholds in nonsurgical and surgical patients. Nicotine replacement therapy (NRT) has shown to modify pain thresholds differently, depending on patients' gender. In fact, although NRT has shown to increase the pain threshold in both smoking and nonsmoking individuals, this effect was observed only in men [9]. Moreover, intranasal nicotine injected in nonsmoking patients undergoing gynecological surgery has demonstrated to decrease pain intensity and opioid consumption in the first 24 hours after surgery [10]. However, a following randomized controlled trial (RCT) in patients undergoing gynecological surgery and receiving a 3-day NRT patch (1 hour before surgery and 2 days after surgery) did not confirm these results [11]. Epidemiological studies have reported that smoking is a risk factor for chronic pain [12].

Experimental trials also demonstrate that anesthetic agents inhibit nAChRs located in the CNS, but it remains uncertain whether smoking status affects anesthetic requirements [4].

Long-term exposure to nicotine can cause tolerance as a result of nAChR desensitization and plastic changes in the central nervous system. These changes are also responsible for somatic and affective nicotine withdrawal symptoms. Because of these long-lasting CNS effects, these symptoms can manifest within a few hours from abstinence and last for several weeks [4, 13] (Fig. 8.1).

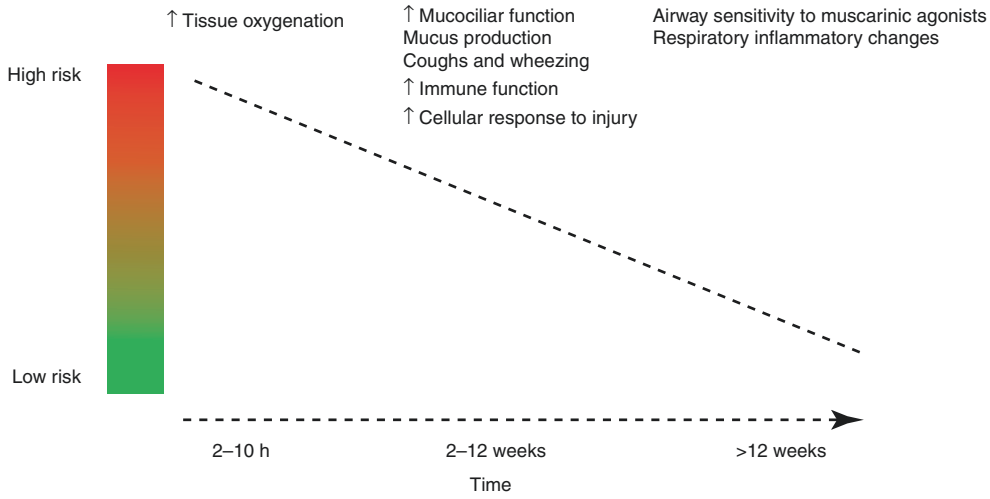


Fig. 8.1 Clinical risk and time required to recover physiologic functions and improve smoke-related symptoms following smoking cessation and preoperative risk. (↑ = improvement. Adapted from [13])

Smoking and Smoking Cessation With and Without Perioperative Interventions: Impact on Clinical Outcomes

Overall Complications and Mortality Smoking is associated with higher postoperative mortality and morbidity [3, 14]. The effect of smoking on postoperative outcomes seems procedure specific, with higher morbidity, reoperation, and readmission rates after cardiovascular and oncologic surgery [15]. This risk is higher in both active smokers and in ex-smokers (the risk in active smokers is higher than in ex-smokers) compared to patients who never smoked [14, 16–18]. It also increases proportionally to the number of pack-years smoked [3, 17]. Overall, preoperative smoking cessation interventions reduce postoperative complications by 60% [19]. A meta-analysis including 21 RCTs and 15 observational trials demonstrated that each additional week of smoking cessation further decreases by 19% the risk of developing complications and that the magnitude of this effect was greater after 4 weeks of smoking abstinence [20].

Cardiovascular Complications Whether or not preoperative smoking is an independent risk factor for major cardiovascular complications still remains controversial. This might explain why many cardiovascular score systems used to predict perioperative cardiovascular risk—except the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) calculator—do not include smoking status. However, data from the ACS NSQIP demonstrate that in 82,304 active smokers undergoing major noncardiac surgery, and propensity matched with 82,304 patients who never smoked, the risk of cardiac arrest, myocardial infarction, and stroke was higher (odds ratio [OR] 1.57, 95% confidence interval [CI], 1.10– 2.25; OR 1.73, 95% CI 1.18–2.53; OR 1.80, 95% CI 1.11–2.92, respectively) [3]. A similar cohort study from the same registry also confirmed that arterial cardiovascular complications were more frequent in active smokers than ex-smokers who quit at least 1 year before the date of surgery [14]. RCTs demonstrating that preoperative smoking cessation reduces cardiovascular morbidity are lacking. One RCT conducted in surgical patients undergoing orthopedic surgery reported that cardiovascular complications were reduced in patients receiving preoperative smoking cessation, but this difference was not significant [21].

Respiratory Complications Several studies have reported that smoking is a risk factor for postoperative pulmonary complications (PPCs). In particular it increases the risk of respiratory failure, unplanned intensive care unit, pneumonia, laryngospasm and bronchospasm, desaturation in post-anesthesia care unit (PACU), and increased need for postoperative respiratory therapy [17]. Smoking status is considered the most preventable preoperative risk factor for reducing PPCs. Some prospective studies, aiming at evaluating the independent predictors of PPC, did not identify preoperative smoking as an independent risk factor for PPCs, suggesting that low-risk smoking patients might not be at increased risk [22].

It must be also considered that it is difficult to establish if the observed increased respiratory morbidity is due to tobacco smoke itself or to the severity of the respiratory disease caused by smoking. However, children without respiratory disease undergoing surgery under general anesthesia and who have been exposed to environmental tobacco smoke also have a higher risk of developing PPCs [23, 24], suggesting that smoke per se can increase the risk of developing PPCs.

Reversibility of the respiratory effects of chronic smoke exposure mainly depends on whether patients have developed a chronic obstructive lung disease. Several observational studies demonstrate that preoperative smoking

cessation for more than 4–12 weeks is associated with a reduction in PPCs [25]. In the past, few underpowered studies demonstrated that in patients undergoing cardiac surgery, the risk of developing PPCs is higher if patients abstained from smoking less than 8 weeks before surgery compared to patients who continue to smoke up to 24 hours before surgery. However, these findings have never been reproduced, and current evidence demonstrates that preoperative smoking cessation is always beneficial, and its effects are more pronounce with longer period of abstinence [4, 20, 26, 27]. The UK National Institute for Health and Care Excellence (NICE) smoking cessation guidelines unrestrictedly promotes preoperative smoking cessation [27]. A recent observational trial conducted in patients undergoing curative lung cancer resection demonstrated that patients actively smoking at the moment of surgery had higher PPCs (22% vs. 2%; $p = 0.004$), higher frequency of intensive care admission (14% vs. 0%; $p = 0.001$), and a longer median hospital stay (6 vs. 5 days; $p = 0.001$). PPCs were not significantly different in patients who quit smoking 6 or more weeks before surgery compared to patients who quit less than 6 weeks. Also, patients who never smoked seemed to have better long-term survival after surgery [28]. Information about smoking cessation interventions (if any) were not reported. Although preoperative smoking cessation interventions aiming at reducing PPCs in high-risk patients have been not specifically studied, rehabilitation programs following major lung resections have shown to facilitate smoking cessation and, although not statistically significant, reduce PPCs (after adjusting for chronic obstructive pulmonary disease [COPD] and smoking); having the intervention tended to reduce the risk of developing a PPC (OR = 0.40, 95% CI 0.13–1.01; $p = 0.07$) [29].

Wound and Bone Healing Sørensen et al. demonstrated that, by pooling 140 cohort studies including 479, 150 surgical patients, smoking increases the risk of wound healing complications. In particular the risk of tissue and wound necrosis (adjusted OR [OR_{ad}] 3.60, 95% CI 2.62–4.93), healing delay and dehiscence (OR_{ad} 2.07, 95% CI 1.53 = to 2.81), surgical site infections (OR_{ad} 1.79, 95% CI 1.57–2.04), wound complications (OR_{ad} 2.27, 95% CI 1.82–2.84), hernia (OR_{ad} 2.07, 95% CI 1.23–3.47), and lack of healing (fistula and bone healing) (OR_{ad} 2.44, 95% CI 1.66–3.58) was higher in smokers compared to non-smokers [18]. Moreover, the risk of wound healing complication was higher in former smokers than in patients who never smoked (OR_{ad} 1.31, 95% CI 1.10–1.56), but lower in former smokers than in patients who never quit (OR_{ad} 0.28, 95% CI 0.12–0.72) [18]. These results were in agreement with the results reported by previously published meta-analysis [20]. Reversing the negative effects of nicotine and carboxyhemoglobin on wound healing could take a few hours, while to reverse the nicotine effects on the tissue and immune response to injury might take longer (months). Sørensen et al.'s meta-analysis also evaluated the impact of smoking cessation interventions on postoperative wound healing complications. The analysis included 4 RCTs including 416 patients undergoing abdominal and orthopedic surgery and utilizing different smoking cessation interventions ranging from low, intermediate, to high intensity. Pooled analysis demonstrated that despite surgical site infections being significantly reduced in patients who received smoking cessation (OR 0.40, 95% CI 0.20–0.83), wound healing complications were not (OR 0.48, 95% CI 0.19–1.25) [18]. Interestingly, among the four trials included the only study that utilized a prolonged and intense smoking cessation intervention (6–8 weeks before surgery of individual counseling, NRT, and weekly follow-up, and continued postoperatively for 10 days), which showed reduction of both wound healing complications and surgical site infections after hip and knee arthroplasty [21]. This study also reported higher preoperative smoking cessation rates (complete abstinence) in the intervention group compared to the control group (60% vs. 6%, respectively) [21]. Similar results were also reported by other meta-analyses [30].

Perioperative Smoking Cessation Interventions: Short- and Long-Term Smoking Cessation Rates

Perioperative nicotine abstinence should be considered a "teachable moment" (i.e., an event that motivates individuals to adopt healthy behaviors that reduce risk [31]) to help patients achieve short- and long-term smoking cessation. Despite being challenging, perioperative smoking cessation was achieved in a significant proportion of surgical patients [19]. In an RCT of 168 patients undergoing non-cardiac surgery, Lee et al. demonstrated that preoperative smoking cessation following an intense cessation program (initiated at least 3 weeks before surgery and including brief counseling by the preadmission nurse, smoking cessation brochures, referral to a telephone quitline, and a free 6-week supply of transdermal nicotine replacement) was achieved in a higher proportion of patients receiving the intervention, compared to patients who did not (14.3% vs. 3%, relative risk [RR] 4.0, 95% CI 1.2–13.7) [32]. Thirty-day smoking cessation rates were also better (28.6% vs 11% RR 2.6, 95% CI 1.2–5.5) [32]. A long-term follow-up of the same trial [32] demonstrated also that long-term smoking cessation at 1 year can be achieved in approximately 25% of surgical patients (RR 3.0, 95% CI 1.2–7.8; $p = 0.018$) [33]. Low-nicotine baseline dependency and randomization to the intervention (smoking cessation) were found to be both successful independent predictors of long-term abstinence. Results did not change if data were adjusted for nicotine dependency [33]. Combined strategies are more successful than single interventions.

Moreover, the success of perioperative smoking cessation depends on the intensity and duration of the intervention. Detailed discussion will follow.

When and Whose Responsibility?

Clinical data suggest that in the perioperative period, nicotine abstinence contributes to reduced postoperative morbidity. Smoking cessation always should be advised before surgery, independently of the timing of the intervention [27]. Although the optimal duration to reverse the adverse effects of smoking and improve postoperative outcomes is currently unclear, longer periods of intense preoperative smoking cessation interventions (3–4 weeks or longer) are associated with better perioperative outcomes, especially less pulmonary, wound healing, and infectious complications [17, 19, 20].

These data highlight the importance of promoting smoking cessation as early as possible in the preoperative period course—ideally at the time of surgical referral or scheduling. Caregivers involved in the perioperative care of patients (surgeons, anesthesiologists, internists, general practitioners [GPs], and nurses) should all recommend smoking cessation before surgery, at every opportunity. Specialized nurses in smoking cessation are also a useful resource, especially in the context of a preoperative clinic. Although the preoperative clinic visit represents an ideal moment to initiate smoking cessation interventions, patients are often seen only few days/weeks before surgery, thereby limiting the utilization of valuable smoking cessation resources. Alternatively, general practitioners who are already aware of the patient's medical history and of the effectiveness of smoking cessation in the general population might play an important role in facilitating smoking cessation in prevision of surgery. GPs have the opportunity to better exploit the preoperative period to promote the importance of preoperative nicotine abstinence and initiate smoking cessation interventions at the time of diagnosis, way before surgical referral [34].

However, several barriers such as perception of lack of effect; lack of clinical time, skills, and professional training; reluctance to raise this issue due to patient sensitivity about smoking; perceived lack of patient motivation; and inability to use effective strategies prevent this practice, especially in the perioperative period [34]. When preoperative smoking cessation is not possible, postoperative nicotine abstinence has also proven benefits to achieve smoking cessation and improve postoperative outcomes [4].

How?

Generally, quitting smoking is difficult and rarely successful even in nonsurgical patients and individuals [35]. From a surgical patient's perspective, the preoperative period is not the easiest and ideal moment to quit smoking. A simple preoperative recommendation could work in some very motivated patients, but it will not be successful in the majority. The awareness of being diagnosed with a certain disease and the wait for the upcoming surgery can generate anxiety and paradoxically increase the number of cigarettes smoked, especially a few days or hours before the operation. This highlights the importance of utilizing specialized resources and personnel to successfully help patients to quit smoking before surgery [36]. The framework of 5As method could provide a systematic approach to identify, assist, and follow up smokers waiting for surgery [37] (Table 8.1).

Table 8.1 The "5 A's" that are the major steps to smoking intervention

1. Ask	Identify and document tobacco use status for every patient at every visit
2. Advise	In a clear, strong, and personalized manner, urge every tobacco user to quit
3. Assess	Is the tobacco user willing to make a quit attempt at this time?
4. Assist	For the patient willing to make a quit attempt, use counseling and pharmacotherapy to help him or her quit
5. Arrange	Schedule follow-up contact, in person or by telephone, preferably within the first week after the quit date

Reprinted from Five Major Steps to Intervention (The "5 A's"). Content last reviewed December 2012. Agency for Healthcare Research and Quality, Rockville, MD. https://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/5steps.html

Monitoring smoking cessation attempts is important, and it can be easily done by using relatively inexpensive, handheld, expired-air CO monitors. CO concentrations above 10% warn for immediate attention.

Perioperative smoking cessation interventions can be divided into counseling or pharmacotherapy.

Counseling

In the perioperative period, a variety of methods can be used to discuss the importance of smoking cessation and to facilitate the achievement of this objective. Counseling should first advise the patient to quit smoking in preparation for surgery, then assist the patient in devising a personalized quit plan, provide practical problem-solving skills, help the patient to obtain social support (e.g., from a spouse), and provide supplemental educational materials (e.g., brochures). These interventions can be delivered by a variety of providers with equal effectiveness. The effectiveness of counseling is independent from gender, ethnicity, age, and different social backgrounds [38]. Advising patients to quit smoking before surgery is the first step. In nonsurgical individuals, a simple advisory has a marginal but important effect on smoking cessations, as it increases quit rates by only 1–3% [39]. Patients with low literacy might find it difficult to understand the importance of smoking cessation. Even a simple and brief (<3 minutes) discussion with the patient about the importance of smoking cessation is useful,

and it increases quit rates [38]. This message also should be delivered and reinforced by clinical nurses working with surgeons or in the preoperative clinic. A dose-response relationship exists between the duration and intensity of the intervention and efficacy. Increasing the amount of behavioral support increases smoking cessation rates by 10–25% [40]. Efficacy also increases by combining different counseling formats [38]. These include in-person individual (face-to-face) or group counseling or telephone counseling. Free Web-based and text messaging cessation support or mobile apps are also available. Telephone counseling can be proactive (the counselor initiates one or more calls to support patients trying to quit smoking or avoid relapse) or reactive (the patient calls a specific service, telephone quitline, hotline, or helplines) [38].

Telephone quitlines are widely available, nationally and regionally. They can be accessed from the community, before and after surgery, without requiring a significant increase in resources. Their efficacy is well proven, and preliminary data show benefits even in patients with severe mental illness in whom smoking cessation is more challenging [41]. Callback counseling enhances the effectiveness of telephone quitlines. Higher quit rates have been observed in patients who received proactive counseling (most of the studies demonstrating benefits included at least two phone calls) compared to patients receiving reactive counseling [42].

Utilization of these community-based interventions might be particularly valuable in surgical patients, as they could eventually unburden GPs and perioperative physicians who frequently work with limited time and resources. Early referral is pivotal to maximize the effect of smoking cessation on postoperative outcomes.

Pharmacotherapy

Several pharmacological agents can be used depending on the timing of the intervention, patient's comorbidities, smoke history (pack-years), patient psychological characteristics, and preference. First-line pharmacologic therapies include NRT, varenicline, and bupropion (Fig. 8.2).

Nicotine Replacement Therapy (NRT) A cigarette contains 10–15 mg nicotine and delivers on average 1 mg nicotine to the smoker [43]. The peak plasma nicotine concentration during smoking is 10–50 ng/mL with about 5% being protein-bound. The half-life averages 2 hours. Genetic variability in nicotine metabolism explains the higher concentrations of nicotine metabolites in black smokers than in white smokers [43]. Plasma nicotine concentra-

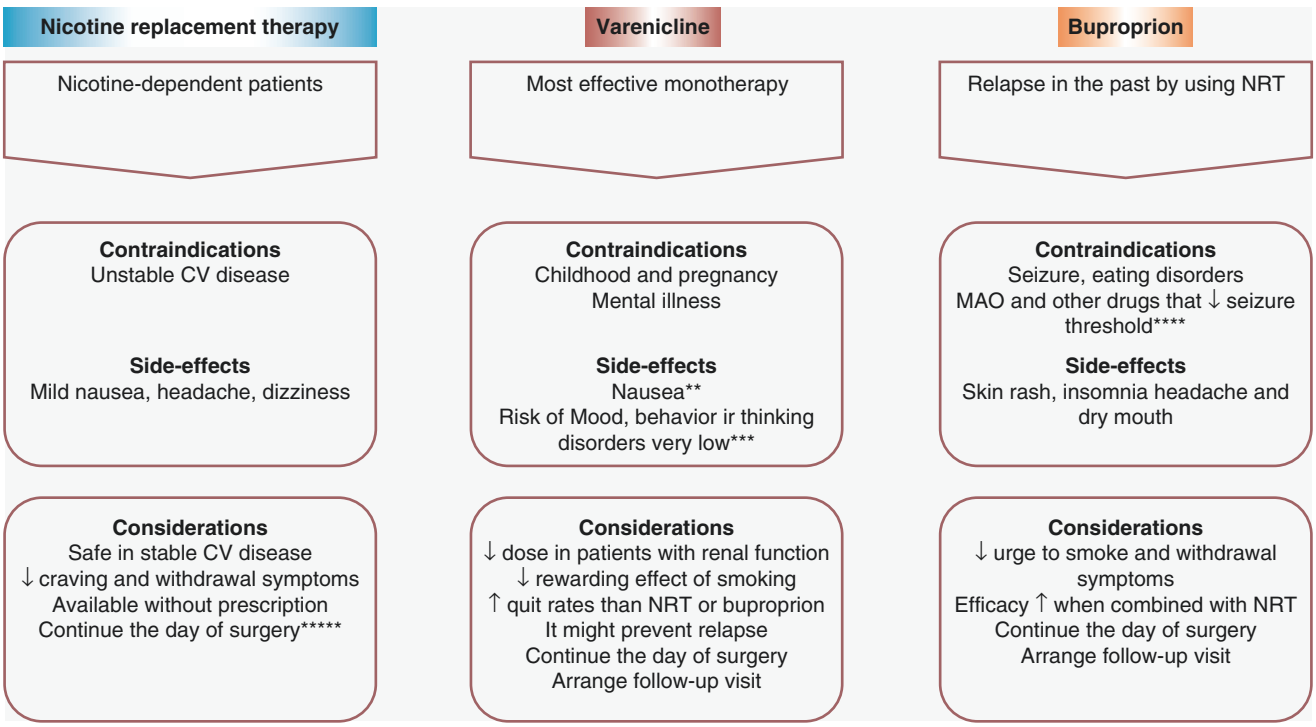


Fig. 8.2 First-line pharmacologic therapies include nicotine replacement therapy, varenicline, and bupropion. CV, cardiovascular; MAO, monoamine oxidase inhibitors; NRT, nicotine replacement therapy. (** Decrease by up-titrating the dose; *** lower than expected; benefits of stop smoking outweigh the risk of varenicline; **** oral hypoglycemic agent, antidepressant; ***** discontinue in patients requiring a vascular graft. ↓ decrease; ↑ increase. Adapted from [44])

tions measured in patients receiving any form of NRT are lower than those observed in active smokers, even when patients do not completely quit [4].

A variety of studies conducted in the nonsurgical general population have well established the effectiveness of NRT. NRT can be delivered with nicotine patches (long-acting effect) and/or though nicotine gum, inhalator, mouth spray, lozenge, sublingual microtablet, and nasal spray (rapid- and short-acting effect) [43, 44]. In the general population, all forms of NRT are effective in increasing smoking cessation rates by 50–70%, independently from the setting, duration of the therapy, and the additional support offered to the individual [45]. In surgical patients, the majority of studies demonstrating an increase in smoking cessation rates used NRT [19]. Moreover, the impact of smoking cessation interventions including NRT on postoperative complications seems to depend on the intensity and duration of the intervention [18–20, 30]. NRT initial dose depends on the number of cigarettes smoked per day (Fig. 8.3 McGill smoking cessation protocol), and NRT products can be used while patients are still smoking. The dose is gradually tapered, and NRT is recommended until 2–3 months after smoking cessation.

Combining a NRT patch with a rapid delivery form is particularly useful in nicotine-dependent patients (smoking within 30 minutes of waking in the morning or smoking more than 10 cigarettes a day [44]) to control withdrawal and craving symptoms [44]. Moreover, combining different NRT formulations (short- and long-acting NRT) is more effective (smoking cessation) than a single NRT intervention [45]. There is also evidence that NRT patch initiated for 2 weeks before quitting smoking is more effective than starting NRT on quit day [44, 45]. Combining different NRT products does not significantly increase nicotine plasma concentrations that are anyway lower than those achieved in patients smoking one pack per day [44, 45].

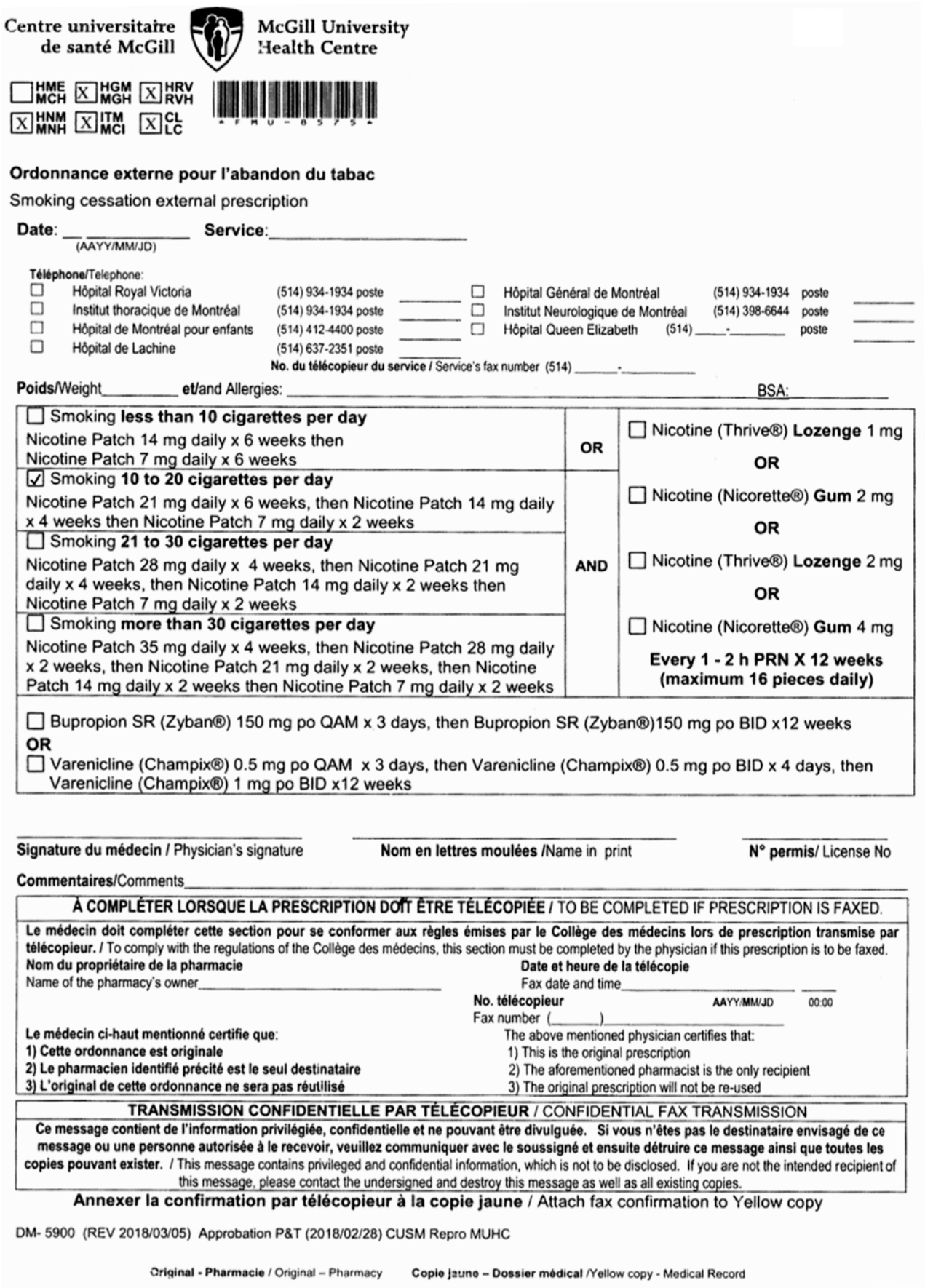
NRT side effects are mild and generally improve over time. They include gastrointestinal symptoms (nausea, vomiting, abdominal pain, diarrhea), headache, and dizziness and depend on the delivery method [43]. An NRT patch can cause skin irritation and disturbed sleep, while an oral formulation can cause sore mouth, heartburn, or hiccups [43, 44]. In the presence of side effects, the NRT dose can be titrated down or changed to another formulation or medication. NRT dependence is rare [43].

Preoperative smoking cessations provide benefits that far outweigh the cardiovascular risk of continuing smoking or of the potential risk of using NRT until surgery [3, 21, 46, 47]. The safety of NRT in patients with stable cardiovascular disease is well established [43]. This is probably due to the fact that adverse events caused by smoking are also due to other constituents present in the cigarette smoke and that peak plasma nicotine concentrations produced by cigarettes are higher than those observed during NRT [4]. Nicotine plasma concentrations of smokers receiving NRT are lower even in patients who do not completely quit smoking before surgery [4]. Moller et al. reported a nonsignificant reduction of cardiovascular complications in surgical patients receiving NRT (0% vs. 10%, $p = 0.07$). Higher heart rate has been observed post tracheal intubation in surgical patients receiving NRT patch compared to patients receiving placebo [48].

Beneficial effects of NRT also have been observed in studies evaluating wound healing [4, 49]. Some studies have also shown that NRT promotes angiogenesis, thus suggesting that NRT does not negatively affect wound healing [4]. On the contrary, the study by Moller et al. demonstrated that preoperative smoking cessation interventions including NRT were particularly beneficial in reducing wound-related complications [21]. Many orthopedic surgeons avoid NRT because of concern that it will impede bone healing. However, clinical trials demonstrating that perioperative NRT negatively affect bone healing compared with smoking tobacco is lacking [43].

Whether to discontinue NRT patches 24 hours before surgery or continue use throughout the entire perioperative period is controversial. Most of the studies demonstrating reduction in complications following preoperative smoking cessation interventions including NRT patch did not interrupt NRT before surgery [18–21, 30]. NICE guidelines suggest discontinuing NRT 24 hours before surgery, in particular for patients undergoing microvascular reconstructive procedures [27].

Varenicline Varenicline is a partial nicotine agonist that has been successfully used to alleviate craving and withdrawal symptoms and to reduce the rewarding effect of smoking [43, 44, 50]. The results of a network meta-analysis found that varenicline is the most effective pharmacological intervention to achieve abstinence (assessed at 6 months or after initiation of the intervention) when compared to NRT alone (OR 1.57; 95% credible interval [CredI] 1.29–1.91) or bupropion (OR 1.59; 95% 95% CredI 1.29–1.96), but not when it was compared to combined NRT interventions (OR 1.06; 95% CredI 0.75–1.48) [51]. Pharmacologic superiority of varenicline as monotherapy to achieve smoking abstinence (assessed at 9–12 weeks after initiation), compared to NRT or bupropion, was also confirmed in a large multicenter RCT [52]. Varenicline is also more effective than NRT and bupropion to achieve short-term smoking cessation, defined as 4 weeks post target quit date [53]. Treatment should be initiated with 0.5 mg per os once a day for 3 days and progressively increased over time (Fig. 8.3). Dosage should be reduced in patients with reduced renal function [44].The most common side effect of varenicline is nausea (mild to moderate) in 30% of users. However, it rarely causes discontinuation, observed only in 3% of the patients [44]. Nausea can be reduced by up-titration of the dose and by consuming the drug with food [44].



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* F M U - 8 5 7 5 *

Ordonnance externe pour l'abandon du tabac

Smoking cessation external prescription

Date: __ _____ (AAYY/MM/JD) **Service**:_____

Téléphone/Telephone:

☐	Hôpital Royal Victoria	(514) 934-1934 poste _____	☐	Hôpital Général de Montréal	(514) 934-1934 poste _____
☐	Institut thoracique de Montréal	(514) 934-1934 poste _____	☐	Institut Neurologique de Montréal	(514) 398-6644 poste _____
☐	Hôpital de Montréal pour enfants	(514) 412-4400 poste _____	☐	Hôpital Queen Elizabeth	(514) ___-_____ poste _____
☐	Hôpital de Lachine	(514) 637-2351 poste _____			

No. du télécopieur du service / Service's fax number (514) _____-_____

Poids/Weight_____ **et**/and Allergies: _____ BSA: _____

☐ Smoking **less than 10 cigarettes per day** Nicotine Patch 14 mg daily x 6 weeks then Nicotine Patch 7 mg daily x 6 weeks	**OR**	☐ Nicotine (Thrive®) **Lozenge** 1 mg **OR** ☐ Nicotine (Nicorette®) **Gum** 2 mg **OR** ☐ Nicotine (Thrive®) **Lozenge** 2 mg **OR** ☐ Nicotine (Nicorette®) **Gum** 4 mg **Every 1 - 2 h PRN X 12 weeks (maximum 16 pieces daily)**
☑ Smoking **10 to 20 cigarettes per day** Nicotine Patch 21 mg daily x 6 weeks, then Nicotine Patch 14 mg daily x 4 weeks then Nicotine Patch 7 mg daily x 2 weeks	**AND**	
☐ Smoking **21 to 30 cigarettes per day** Nicotine Patch 28 mg daily x 4 weeks, then Nicotine Patch 21 mg daily x 4 weeks, then Nicotine Patch 14 mg daily x 2 weeks then Nicotine Patch 7 mg daily x 2 weeks		
☐ Smoking **more than 30 cigarettes per day** Nicotine Patch 35 mg daily x 4 weeks, then Nicotine Patch 28 mg daily x 2 weeks, then Nicotine Patch 21 mg daily x 2 weeks, then Nicotine Patch 14 mg daily x 2 weeks then Nicotine Patch 7 mg daily x 2 weeks		

☐ Bupropion SR (Zyban®) 150 mg po QAM x 3 days, then Bupropion SR (Zyban®)150 mg po BID x12 weeks
OR
☐ Varenicline (Champix®) 0.5 mg po QAM x 3 days, then Varenicline (Champix®) 0.5 mg po BID x 4 days, then Varenicline (Champix®) 1 mg po BID x12 weeks

Signature du médecin / Physician's signature **Nom en lettres moulées** /Name in print **N° permis**/ License No

Commentaires/Comments_____

À COMPLÉTER LORSQUE LA PRESCRIPTION DOIT ÊTRE TÉLÉCOPIÉE / TO BE COMPLETED IF PRESCRIPTION IS FAXED.

Le médecin doit compléter cette section pour se conformer aux règles émises par le Collège des médecins lors de prescription transmise par télécopieur. / To comply with the regulations of the Collège des médecins, this section must be completed by the physician if this prescription is to be faxed.

Nom du propriétaire de la pharmacie
Name of the pharmacy's owner_____

Date et heure de la télécopie
Fax date and time_____ ____
No. télécopieur AAYY/MM/JD 00:00
Fax number (_____)_____

Le médecin ci-haut mentionné certifie que:
1) Cette ordonnance est originale
2) Le pharmacien identifié précité est le seul destinataire
3) L'original de cette ordonnance ne sera pas réutilisé

The above mentioned physician certifies that:
1) This is the original prescription
2) The aforementioned pharmacist is the only recipient
3) The original prescription will not be re-used

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Fig. 8.3 McGill smoking cessation protocol. (developed by Dr. Sean Gilman, director of the McGill Smoking cessation program, and his team; with permission)

Sleep disorders such as insomnia or abnormal dreams are also common. Post-marketing reports have described depression, agitation, changes in behavior, and suicidal ideation with the use of varenicline. However, the results of a meta-analysis including 17 RCTs did not confirm these findings in patients with and without mental illness [54]. Moreover, the results of a recent large multicenter RCT further validate the safety of varenicline [52]. Current evidence does not indicate cardiovascular toxicity [43].

Two RCTs evaluating the perioperative efficacy of varenicline in patients undergoing noncardiac surgery demonstrated that varenicline is effective in achieving long-term smoking cessation, when compared to placebo [55] or to brief nonpharmacological smoking cessation interventions [55, 56]. However, it did not impact postoperative outcomes [19].

Bupropion Bupropion is an antidepressant, and it could be administered in patients with nicotine addiction and depressed mood. It decreases the urge to smoke and symptoms of withdrawal. Its effectiveness improves when used together with NRT. Dosing of bupropion is 150 mg per os daily for 3 days followed by 150 mg per os twice daily for up to 12 weeks, and it is usually started 1–2 weeks before a patient starts to quit [4]. It is contraindicated in patients with seizure, with eating disorders, or taking monoamine oxidase. Caution should be used in patients who take medications that reduce the seizure threshold such as hypoglycemic agents and antidepressants [44].

The risk of neuropsychiatric and cardiovascular toxicity in individuals using bupropion is not higher than those receiving placebo [51]. One small RCT of surgical patients treated with bupropion as monotherapy to achieve preoperative smoking cessation demonstrated that bupropion is useful to reduce the number of cigarettes smoked before surgery, reduce end-expired CO, increase arterial oxygen saturation on pulse oximetry before surgery, and increase smoking cessation rates at 3 weeks but not 6 weeks, after surgery [57].

Other Pharmacological Agents and Methods A variety of other pharmacological agents and methods have been used to achieve smoking cessation, but their efficacy is not proven in surgical patients. In particular, the efficacy of electronic cigarettes to achieve smoking cessation is marginal compared to smokers receiving placebo, and it is not superior to results reported with approved pharmacological agents [58]. However, they do not produce carcinogens and toxins as conventional cigarettes. Perioperative studies investigating the ability of electronic cigarettes to achieve smoking cessation are lacking. Due to the lack of safety data in surgical patients, electronic cigarettes cannot be recommended as a strategy to achieve preoperative smoking cessation, and patients already using electronic cigarettes should be encouraged to substitute nicotine assumption with NRT products before surgery [58, 59].

Duration and Intensity of Preoperative Smoking Cessation Interventions, Smoking Cessation Rates, and Complications

The best strategy to support preoperative tobacco abstinence is unknown, and individualized interventions are more likely to be effective. In the general population, a combination of counseling with pharmacotherapy increases smoking cessation rates (RR 1.82, 95% CI 1.66–2.00) [42, 44, 60]. These data are also confirmed in surgical patients. Overall, preoperative prolonged (4 weeks or longer) and intense (pharmacological therapy combined with preoperative counseling) interventions are very effective to increase preoperative and long-term smoking cessation rates, compared to patients not receiving any interventions (RR 10.76, 95% CI 5.55–25.46 and RR 2.96, 95% CI 1.57–5.55, respectively) [19, 59]. Brief preoperative smoking interventions (without follow-up) also increase preoperative and long-term smoking cessation rates but not to the same extent (RR 1.30, 95% CI 1.14–1.46, and RR 2.29, 95% CI 1.14–1.61, respectively), compared to patients not receiving any interventions [19, 59]. In contrast, postoperative complications are reduced only by preoperative intense smoking cessation interventions, by almost 60% (RR 0.42, 95% CI 0.27–0.65) [19, 59].

Finally, it might be possible that preoperative smoking cessation interventions are more beneficial in certain surgical populations than others, as the impact of smoking on postoperative outcomes seems to be procedure specific [15]. Current benefits have been mainly proven in patients undergoing orthopedic and abdominal procedures, while studies evaluating the efficacy of preoperative smoking cessation interventions in patients undergoing thoracic or cardiac surgery (high prevalence of smoking and high risk of pulmonary complications) are lacking.

Withdrawal Syndrome

Neurobiology of nicotine withdrawal syndrome is complex, as nicotine modulates the release of several neurotransmitters [61]. Withdrawal syndrome symptoms are rare postoperatively and are more frequent when the abstinence period is forced rather during the stressful perioperative period [4]. Thus, routine NRT is not indicated in every smoker undergoing surgery [4]. However, it can significantly help to reduce the number of cigarettes smoked per day once patients are discharged from the hospital [4].

Alcohol Cessation

It is well recognized that alcohol abuse is a risk factor for several chronic diseases and that hazardous drinking increases the risk of postoperative morbidity. Although withdrawal from alcohol partially reverses organic dysfunction in

nonsurgical patients, perioperative alcohol cessation strategies have been infrequently studied and rarely offered as routine surgical care.

Alcohol abuse disorders in surgical patients (defined by the consumption of at least five drinks per day and identified by a self-reported alcohol intake questionnaire) have been reported ranging from 7% to 49%, depending on gender and diagnosis [62]. Alcohol dependency is found in one out of ten hospitalized surgical patients, in 25% of trauma patients, and up to 50% in patients with certain cancers [63]. Moreover, alcohol use disorders are underestimated when assessed in the preoperative setting, especially in women and younger patients [64]. The use of preoperative screening tools, such as the CAGE ("cut down," "annoyance," "guilt," and "eye-opener") and AUDIT (Alcohol Use Disorders Identification Test) questionnaires, together with the use of certain laboratory testing, can be useful to better identify surgical patients with alcohol dependency [63]. A recent Cochrane meta-analysis including surgical patients undergoing elective and emergency surgery defined "risky drinking" patients with an alcohol consumption equivalent to more than 3 alcoholic units (AU)/day or 21 AU/week (with 1 AU containing 12 grams of ethanol) with or without symptoms of alcohol abuse or dependency. This corresponds to the amount of alcohol associated with increased postoperative complication rates in most clinical studies [65]. Higher cutoff (alcohol intake of more 60 g of ethanol per day, five drinks or 1.5 l of beer), associated with at least double the complication and mortality rates, also has been used [63].

Alcohol Abuse and Cessation in the Perioperative Period: Pathophysiologic Changes and Impact on Clinical Outcomes

High-moderate quality of evidence suggests that alcohol overconsumption is associated with increased morbidity, in particular infections, cardiopulmonary complications, bleeding and delirium, withdrawal syndrome, and prolonged intensive care unit stay [63, 66]. This is probably due to alcohol-induced organ dysfunction and to the stronger surgical stress response observed in alcohol-abusing patients undergoing surgery. In fact, the magnitude of the stress response to surgery in patients who continue drinking alcohol until surgery is greater than those who quit 4 weeks before surgery. As a consequence, preexisting subclinical organ dysfunctions possibly present in these patients could be further aggravated [13, 67, 68]. Interestingly, in alcohol-abusing surgical patients undergoing gastrointestinal surgery, treatment with low-dose continuous infusion of intravenous morphine (15 mcg/h) reduced postoperative plasma cortisol and preserved cellular immune function. This intervention was also associated with lower pneumonia rates and shorter intensive care unit stay [69].

Alcohol affects the cell-mediated immune response, in particular the delayed-type hypersensitivity (DTH). Studies demonstrate that DTH is already impaired in alcohol-abusing surgical patients [62, 69] and that DTH is associated with higher risk of surgical site infections [62]. A small RCT found that in alcohol-abusing patients, 4 weeks of alcohol abstinence before colorectal surgery improves DTH preoperatively, and this is associated with less postoperative complications than patients who continued drinking until surgery (31% vs. 74%; $p = 0.02$, respectively) [67]. However, in this study infectious complications were not reduced. A recent meta-analysis including 13 observational studies and 5 RCTs confirmed that surgical patients consuming a total of 50 ml spirits 40%, or 150 ml wine 13%, or 500 ml 4% beer or alcopop (a ready-mixed drink containing alcohol) of alcohol per day have a higher risk of developing postoperative surgical site infections [65]. Preoperative abstinence of 4 weeks reduces such risk [13, 70] (Fig. 8.4).

Asymptomatic preoperative cardiac dysfunction has also been reported in alcohol-abusing patients scheduled for surgery [66]. In a small prospective non-RCT, asymptomatic surgical patients scheduled for colorectal surgery

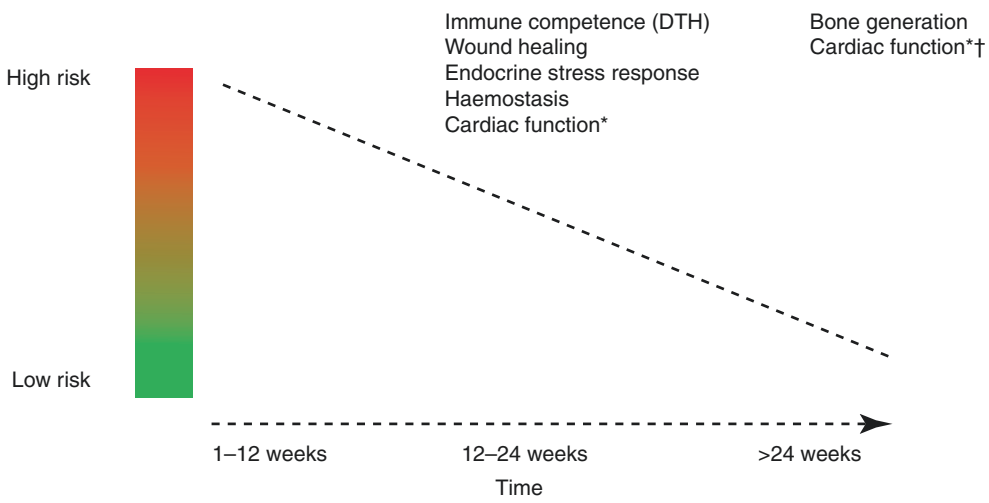

Fig. 8.4 Clinical risk and time required to recover physiologic functions and improve alcohol-related symptoms following preoperative alcohol cessation. (∗ Without symptoms; † with severe failure. Adapted from [13])

and who were drinking at least 60 g of alcohol per day had lower preoperative left ventricle ejection fraction (although within a normal range) than appropriately matched surgical patients who were consuming below 25 g of alcohol daily. The former patients also had a higher incidence of postoperative arrhythmia [66]. Four-week preoperative alcohol abstinence has also shown to reduce postoperative myocardial ischemia [67].

Hemostasis is also influenced by alcohol, as demonstrated by prolonged bleeding time observed in alcohol-abusing surgical patients [66–68]. However, chronic alcohol exposure also negatively affects coagulation and fibrinolysis, and this might further predispose to perioperative bleeding [66].

The results of the latest Cochrane systematic review evaluating the efficacy of perioperative alcohol interventions demonstrated that perioperative alcohol cessation is feasible, safe, and effective. This systematic review and meta-analysis included three small RCTs: one of patients undergoing colorectal surgery and two of patients undergoing orthopedic surgery. The intervention was initiated and terminated preoperatively in two trials and postoperatively for 6 weeks in one trial. All trials included intense interventions, including pharmacological strategies, patient education, and relapse prophylaxis. The pool analysis demonstrated that preoperative alcohol cessation decreases postoperative complications (RR 0.62, 95% CI 0.40–0.96). All three studies aimed at achieving alcohol cessation in the perioperative period. Overall, patients receiving perioperative alcohol cessation interventions were approximately eight times more likely to successfully achieve abstinence (RR 8.22, 95% CI 1.67–40.44; $p = 0.01$) and to reduce alcohol consumption. There was no effect on length of hospital stay and mortality [65].

Perioperative Alcohol Cessation Strategies

Counseling

In the primary care setting, brief interventions, ranging from 1 to 30 minutes, have shown to decrease alcohol by 38 g per week, especially in men (mean difference, 95% CI −54 to −23) [71]. These include motivational, ambivalence-accepting, and non-confronting conversations, in person or computer-based [63]. Perioperative counseling should discuss the risks of continuing alcohol consumption before surgery, discuss the importance of preoperative alcohol cessation, record baseline alcohol intake, ideally schedule weekly meetings during which alcohol consumption is recorded, and provide information on how to manage immediate withdrawal symptoms [13]. About 80% of patients who have been informed about the higher risk of complications are highly motivated in reducing alcohol intake but also seek hospital support [13]. Telephone helplines are also available. Consulting a psychiatrist or substance abuse specialist might be useful to plan a perioperative detoxification program [63].

Pharmacotherapy

Benzodiazepines are mainly prescribed to manage alcohol withdrawal symptoms. Alpha-2 agonists and neuroleptic agents also have been utilized in hospitalized patients [63]. Withdrawal symptoms are frequent, they can be life-threatening, and they can manifest even before a patient is completely sober. After surgery, early recognition is essential as higher mortality rates have been reported in patients who have mistreated alcohol [72]. Medications to support alcohol abstinence such as disulfiram (e.g., 800 mg per os taken during controlled supervision twice per week, until the week before surgery [67]) and/or B vitamins could be prescribed based on patient's preferences. Disulfiram should not be administered when contraindicated and unless blood or air alcohol concentrations have been proven to be zero [13]. Its safety has been demonstrated, and it does not affect craving or withdrawal symptoms [13].

Conclusions and Main Findings

- Smoking and alcohol overconsumption induce several organ dysfunctions that predispose to postoperative complications.
- Longer periods of preoperative smoking cessation abstinence are associated with better outcomes.
- Caregivers involved in the perioperative care of patients (surgeons, anesthesiologists, internists, GPs, and nurses) should all recommend smoking and alcohol cessation before surgery, at every opportunity, and provide assistance when possible.
- Prolonged (4 weeks or longer) and intense (combined counseling and pharmacotherapy) preoperative smoking cessation programs significantly increase preoperative and long-term smoking cessation rates and reduce postoperative complications, in particular PPCs, infections, and wound healing complications (high-moderate quality of evidence).
- Prolonged and intense perioperative alcohol cessation programs increase alcohol cessation rates and decreased complications (low quality of evidence based only on three small RCTs).
- Preoperative smoking and alcohol cessation interventions are infrequent in clinical practice.
- Smoking and alcohol cessation should be initiated as early as possible in the preoperative period course, ideally at the time of surgical referral or scheduling.
- Lack of training, skills, time, and resources is the main factor limiting clinical implementation.

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Preoperative Medical Optimization

9

Matthias Stopfkuchen-Evans

Introduction

Over the last decade, preoperative testing centers have become the cornerstone for preoperative evaluation of patients presenting for elective surgery. This was aimed to provide appropriate information about comorbidities to the surgeon and anesthesiologist in a timely manner and to reduce last-minute cancelations due to missing reports or the need for further testing. These clinics have oftentimes limited their activity to collecting data on patients but have fallen short on analyzing and optimizing patients whenever possible. With the expansion of the enhanced recovery after surgery (ERAS) principle to include preoperative optimization of medical comorbidities and improving the patients' resilience to surgical and perioperative stress through improving cardiovascular fitness, pulmonary reserve, nutrition, and psychological strength, early experience shows encouraging data on patients becoming surgically fit before undergoing oftentimes invasive and high-risk procedures. This chapter aims at summarizing current evidence for the utility of assessing the perioperative risk and preoperative optimization of modifiable medical comorbidities before elective surgery.

Who Should Be Assessed?

In an ideal society, population health is managed so that everyone with asymptomatic chronic conditions of the cardiovascular, respiratory, metabolic, or endocrine systems, among others, is optimized so that the disease state is stable and controlled. Blood pressure is well managed; HbA1C is within acceptable range; asthma and chronic obstructive pulmonary disease (COPD) and emphysema are well controlled; obstructive sleep apnea (OSA) is treated; and patients exercise regularly, eat well, and are free from psychological stressors such as anxiety or depression. Should the need for an operation arise, patients' records are reviewed, and the patient is enrolled in an evidence-based perioperative pathway. The review can be done remotely in most cases as little or no modification is needed, and it suffices that the patient receives instructions regarding the perioperative management. Only patients deemed high risk, whose chronic conditions are decompensated or are poorly managed, need to be seen, assessed, and optimized where this is possible. A list of optimizable conditions is presented in Table 9.1.

Table 9.1 Modifiable risk factors

Anemia
Diabetes
Nutrition
Heart disease
Chronic obstructive pulmonary disease (COPD)/emphysema
Coagulation
Obstructive sleep apnea (OSA)
Substance use, i.e., alcohol, smoking, recreational marijuana
Activity
Mental health
Chronic pain

Timing

Patients should be medically assessed as soon as surgery is contemplated. This is important for two reasons. First, it will allow to objectively include preexisting conditions into the overall risk assessment of the procedure, its expected outcome, and how this compares to alternative means of treatment, such as non-operative or even palliative care. A patient's thorough knowledge of the estimated risk of the procedure and its expected outcome is key to collaborative decision-making (shared decision-making) and may affect it [1]. Second, early assessment of the patient's condition allows optimization of modifiable problems such as preexisting anemia, malnutrition, and

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poorly controlled medical conditions such as hypertension, arrhythmias, or diabetes. The patient can also be more effectively counseled regarding lifestyle modifications such as smoking cessation including marijuana use, decrease of alcohol consumption, targeted physical activity for improved cardiopulmonary fitness and resistance strength, as well as relaxation techniques to decrease stress and anxiety (prehabilitation; see Chap. 10). Additionally, regulating bodies, such as The Joint Commission in the United States, increasingly mandate that surgical consents contain information about the expected outcome of the proposed procedure as well as data about how likely this outcome would actually occur—in other words, a quantification of the likelihood of the procedure to not achieve its intended outcome. Patient factors have significant influence on complications and adverse outcomes, which should be another motivation to optimize and improve a patient's condition before elective surgery and to prognosticate as accurately as possible a patient's propensity for complications in order to facilitate shared decision-making.

Patient Risk Assessment

Patients present with modifiable and non-modifiable problems (Fig. 9.1) [2] that influence the perioperative risk of suffering complications, delayed recovery, or death. Non-modifiable factors such as age, gender, or genetics affect risk scoring systems and, hence, a patient's individual risk undergoing the contemplated procedure. They therefore should be assessed utilizing validated risk indices (Table 9.2). When it comes to estimating cardiopulmonary reserve, a recent publication has questioned the veracity of using a metabolic equivalents (METs) scale given the lack of correlation with the propensity for complications [3]. The inevitable subjectivity whether a patient meets the requirement of four METs might be to blame. Additionally, the "reward" of making this artificial threshold—and forfeiting the necessity for further assessment of functional reserve with more objective tools such as cardiopulmonary exercise testing (CPET)—may have served as an incentive in preoperative clinics. Whether risk assessment alone or its combination with optimization of medical problems results in improved outcomes remains to be proven. It seems natural, however, that preoperative medical optimization improves outcomes given the strong association of numerous conditions with postoperative complications.

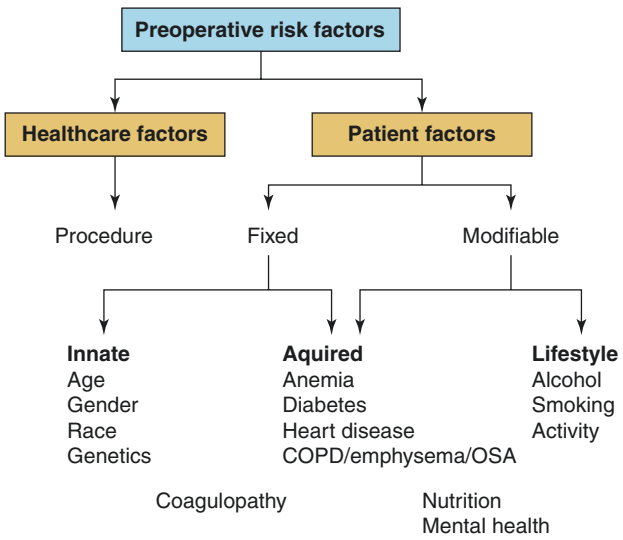

Fig. 9.1 Preoperative risk factors. (Modified after Aronson [2])

Optimization of "Non-modifiable" Factors: Genetics, Age, Gender, and Race

Genetics

Fragiadakis et al. recently showed that signaling behavior of a network of innate immune cells measured before surgery predicts surgical recovery, whether patients recovered "easily" from major surgery such as hip joint replacement or whether their recovery was prolonged with lasting impairment of mobility, fatigue, and pain [4]. While this knowledge at this point relates to non-modifiable phenomena and is only in an early, preclinical stage, it is conceivable that it will inform better planning for a given procedure and that it enables more accurately setting expectations. With better understanding and improvements in technology, one could expect that at some point, not only predicting recovery but modifying and optimizing a patient's path of recovery through measured interventions of the molecular drivers of recovery could become reality. Similarly, significant interindividual differences exist in the metabolism of medications commonly used in the perioperative period, such as opioid and non-opioid analgesics, anticoagulants, antiemetics, or beta-blockers. Having individualized, patient-specific pharmacogenomic information available would inform more targeted treatment and help to reduce unwanted side effects of medications that are less well tolerated given the patient's individual pharmacogenetic profile [5] (see also Chap. 13).

Age

Even though age per se cannot be modified, patients in certain age groups bear specific risks associated with the age group. Particularly, old age and, more specifically, frailty are associated with complications, longer hospital stay, and discharge to long-term care facilities among other problems [6].

Table 9.2 Scoring systems for surgery

Test	Predicting	Scoring	Evidence level	Recommendation
P-POSSUM	Mortality and morbidity	12 physiological and 6 operative variables	High	Strong
ACS NSQIP	Mortality and morbidity	18 physiological and 3 operative variables	High	Strong
Lee index	Perioperative cardiac complications	6 preoperative risk factors	Moderate	Strong
Cardiovascular risk calculator	Myocardial infarct or cardiac arrest	4 preoperative clinical factors and 1 operative variable	Moderate	Strong
Cardiopulmonary exercise testing (CPET)	Perioperative complications	Aerobic exercise—AT and VO2 max	Moderate	Strong
Cardiopulmonary exercise testing (CPET)	Selecting patient's suitability for surgery	Aerobic exercise— AT and VO2max	Moderate	Moderate
General surgery acute kidney injury risk index	Acute kidney injury	11 preoperative clinical factors	Moderate	Moderate

P-POSSUM Portsmouth-Physiological and Operative Severity Score for the enumeration of Mortality and morbidity, *ACS NSQIP* American College of Surgeons National Surgical Quality Improvement Program, *AT* aerobic threshold

Emergency surgery increases this risk even further, so that as recent as in 2014 it was proposed to not even offer surgery as an option to this high-risk group of frail elderly patients [7]. Mrdutt and colleagues report that frailty was associated with increased morbidity, mortality, and health-care cost across a large variety of in- and outpatient procedures, both emergent and elective [6]. However, neither group considers nor reports the impact of an enhanced recovery program on this at-risk population. With the application of the ERAS methodology, and the aggregation of marginal gains, even frail elderly patients can undergo major procedures with an acceptable risk profile [8]. The assessment of frailty- and age-associated risk should inform decision-making about the surgical care proposed and trigger the enrollment in specialized multifaceted perioperative pathways to optimize the outcome and minimize harm in this at-risk population. It is feasible to imply that involving specialists such as geriatricians in the development and continuous improvement of perioperative pathways improves recovery and outcomes, mitigates risk, and increases the likelihood of the individual to return to their pre-surgical functional state and living circumstances. However, which interventions specifically improve the risk that frailty bears have not been well enough established. Enhanced recovery after surgery (ERAS) pathways not only aim at reduction of perioperative stress, which is particularly poorly tolerated by frail elderly patients, but also support regaining important functions such as early oral alimentation and mobilization while preventing harm and are well suited for this high-risk group of surgical patients [9].

Gender and Race

Gender and race are important aspects of perioperative assessment and care given the ongoing disparities in care and care outcomes [10]. Even though these are so-called "non-modifiable" factors, being cognizant of care disparities and implicit bias should be a first step in reducing and eventually eliminating inequalities in health-care delivery based on race or gender [11]. More work is needed to better define gender and race disparities as they relate to perioperative medicine and outcomes as well as proposing steps to close this gap.

Optimization of Modifiable Factors

Numerous medical conditions have been identified that negatively impact a patient's perioperative course and recovery that can be positively influenced, improved, or ameliorated with relatively little cost and effort, provided there is a window of opportunity of ideally 3–4 weeks. However, as little as 2 weeks might suffice. Among such conditions are anemia and nutritional deficits. Comorbidities such as diabetes, hypertension, cardiovascular disease, chronic obstructive pulmonary disease (COPD) and emphysema, anxiety, and lack of physical activity should be optimized. Chronic pain and obstructive sleep apnea (OSA) are unlikely to be improved in such a short timeframe; however, it is important to make the care team aware of these problems since those patients require special consideration when planning an operation as well as their postoperative disposition, monitoring, and treatment.

Anemia

Preoperative anemia predicts perioperative morbidity and mortality. It has been associated with increased risks for cardiac events, respiratory failure, acute kidney injury, infections, and deep vein thromboses (DVTs) [12]. The vast majority of anemias can be traced back to iron deficiency.

However, oral iron substitution is oftentimes insufficient to restore iron, especially in the setting of chronic inflammation due to underlying conditions such as cancer, chemotherapy, or injury. Intravenous iron substitution is effective in raising hemoglobin levels within as little as 2–3 weeks. Whether normalizing preoperative hemoglobin levels improves outcomes is currently uncertain. It does, however, decrease the need for allogenic blood transfusion, which traditionally has been associated with a higher propensity for complications and adverse outcomes as well as less favorable oncologic outcomes. The latter is currently under re-evaluation, however, since careful controlling for cofounders may prove this association to be unfounded [13]. This topic is discussed in more detail in Chap. 7.

Nutrition

Perioperative malnutrition is an independent predictor of poor postoperative outcomes [14]. Yet, preoperative malnutrition can be easily identified and corrected [15]. See Chap. 6 for details.

Diabetes

Chronic diabetes causes endothelial dysfunction, autonomic dysregulation, and macro- and microangiopathy and, hence, puts patients at heightened perioperative risk for surgical site infections, thromboembolic events, cardiovascular complications, renal insufficiency, and prolonged length of stay. The degree of HBA1C elevation predicts postoperative hyperglycemia and complications even within an established ERAS program [16] and, therefore, should be measured and, if elevated, glycemic control should be improved preoperatively. Currently, a HbA1C threshold of <8% is recommended. In a systematic review and meta-analysis, Biancari and Giordano suggest that at least for open heart surgery, the acceptable preoperative HbA1C should be as low as 6–7% [17]. This raises the question whether there is an aspect of procedure specificity to preoperative optimization. Whether surgery should be postponed until acceptable HbA1C targets are reached must be confirmed in robust prospective studies and may not always be feasible for cancer surgery or urgent revascularization procedures. This underlines the importance of assessing the patient as early as surgery is contemplated. A robust plan for perioperative glycemic control should be formulated. This may require referral to a diabetes specialist. Diabetes consultation is associated with better intra- and postoperative glucose control. Not only are hyperglycemic events less likely, but even more importantly, less hypoglycemia occurs postoperatively [18]. Intraoperatively, blood glucose levels should be less than 180 mg/dl, while hypoglycemia is avoided. Postoperatively, blood glucose should be maintained between 80 mg/dl and 150 mg/dl. Nothing per mouth phases should be minimized according to current guidelines (American Society of Anesthesiologists/European Society of Anaesthesiology [ASA/ESA]). There is little reason to assume that patients with diabetes have obligatory gastric paresis and should be treated differently than non-diabetic patients in regard to fasting times. Whether carbohydrate loading for diabetic patients reduces complications such as postoperative nausea and vomiting (PONV) or anxiety and enhances well-being, reduces perioperative stress, and improves outcomes is unclear at this time. When instructing the patient regarding modifying their antidiabetic regimen, the additional carbohydrate burden should be considered. If no carbohydrate load is prescribed, oral antidiabetic medications are withheld on the day of surgery. Intermediate and long-acting injectable insulin should be dose-adjusted starting the night before surgery to 75% of the usual dose. If taken in the morning, on the day of surgery, the dose should be reduced by 50% (see Fig. 9.2). Jorgensen and co-workers have demonstrated that with a fast-track methodology including regional anesthesia, opioid-sparing multimodal analgesia, early oral alimentation, and mobilization, outcomes after total joint replacement surgery did not differ significantly in type 2 diabetic patients compared to their non-diabetic control group [19].

Hypertension

High blood pressure is common and associated with life-threatening comorbidities such as ischemic heart disease, diastolic and systolic heart failure, renal impairment, and cerebrovascular disease. In a random cohort, reliable blood pressure control is difficult to achieve. It is estimated that almost 30% of adults in the United Kingdom have hypertension, but only about 10% are well controlled according to current guidelines. The perioperative risk of hypertension is on a continuum, with higher blood pressure values representing higher risk for complications. Mild to moderate preoperative hypertension is probably not a major risk factor for complications [20]. However, in a large observational study, diastolic hypertension defined as >90 mm Hg was associated with increased mortality in all patient groups [21]. In the same study, preoperative *hypo*tension, particularly *diastolic* hypotension, was statistically significantly associated with increased postoperative mortality. Here, the risk started to increase when blood pressure decreased below 119 systolic and 63 diastolic, respectively. The risk increased with even

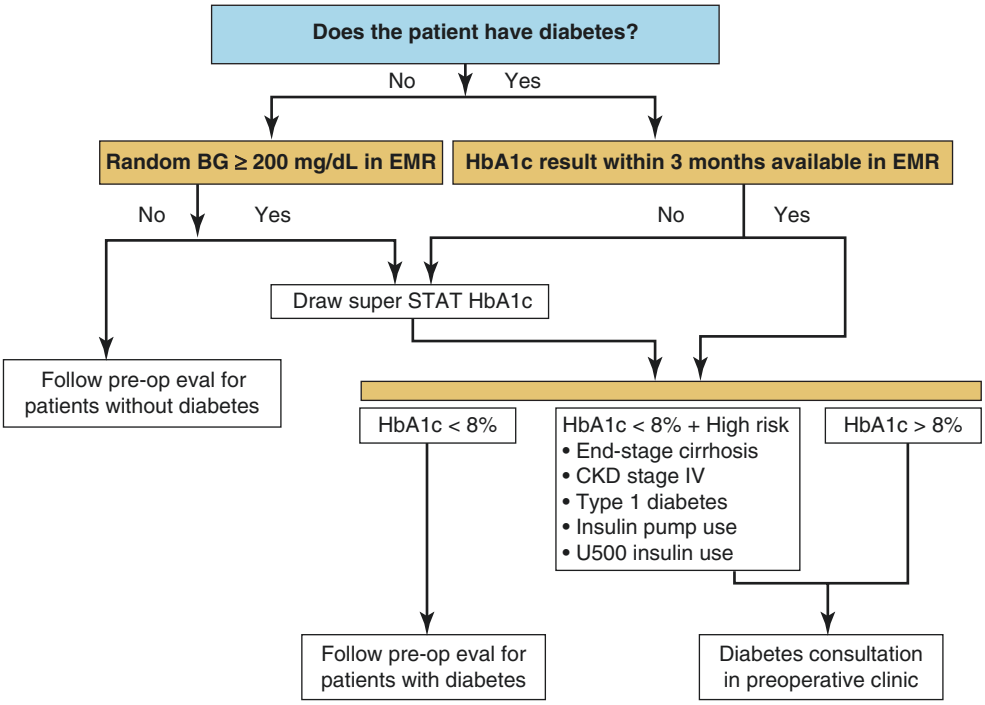

Fig. 9.2 Algorithm for preoperative treatment of diabetes

lower blood pressure values. This was confined to the elderly patient group (age > 65). The definition of hypertension is dependent on age as well as the existence of comorbidities such as ischemic heart disease or chronic renal impairment. In the United States, JNC 8 guidelines [22] recommend treatment for patients age 60 years and older without diabetes or chronic renal disease to maintain blood pressures less than 150/90 mm Hg. Utilizing the correct technique to measure blood pressure is emphasized [23]. In the ambulatory setting, the patient should be seated or in the supine position, with the blood pressure cuff at the level of the patient's right atrium. The cuff's width should be at 37–50% of the patient's arm circumference. It should be placed on bare skin, but shirt sleeves should not be rolled up because this may create a tourniquet effect. Oscillometric measurements should be given preference over auscultatory methods.

It is important for the perioperative care team to be aware of usual blood pressure values, given the risk for myocardial injury or acute kidney injury after noncardiac surgery when perioperative blood pressure is allowed to drop below 20% of usual values intra- and postoperatively [24]. Generally, antihypertensive medications such as beta-receptor blocking agents and calcium channel blockers should be continued. Due to concern of perioperative hypotension, angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) should probably be held on the day of surgery but resumed as soon as feasible [25]. It is our practice to also hold diuretics on the day of surgery unless prescribed for heart failure.

Cardiovascular Disease

Preoperative optimization of patients with cardiovascular disease is oftentimes taken as synonymous with preoperative risk assessment of patients undergoing noncardiac surgery. It is beyond the scope of this text to present an in-depth discussion of the latest American College of Cardiology/American Heart Association (ACC/AHA) guidelines [20], which discuss detailed strategies to assess and reduce the cardiovascular risk of patients undergoing noncardiac surgery. An algorithm to assess the cardiovascular risk of patients presenting for noncardiac surgery is presented in Fig. 9.3. The revised Lee cardiac risk index is frequently utilized to estimate the risk of suffering from cardiac events perioperatively (Table 9.3). Even though the focus has traditionally been on ischemic heart disease, other cardiac conditions such as heart failure pose a significantly greater risk for major adverse cardiac events (MACE) in the perioperative period when undergoing noncardiac surgery [26]. Ischemic disease is the major cause for systolic heart failure, whereas hypertension is the dominating reason for diastolic heart failure. Heart failure increases the perioperative mortality by a factor of 3–5 to about 10% in 30 days. Complications are equally increased, especially in decompensated failure. It is important to note that recommendations to reduce the risk of heart failure in patients presenting for surgery include correction of anemia and nutritional deficit as well as optimization of kidney and liver function and volume status, by now all familiar items in the ERAS methodology [27]. Elevated levels of C-reactive

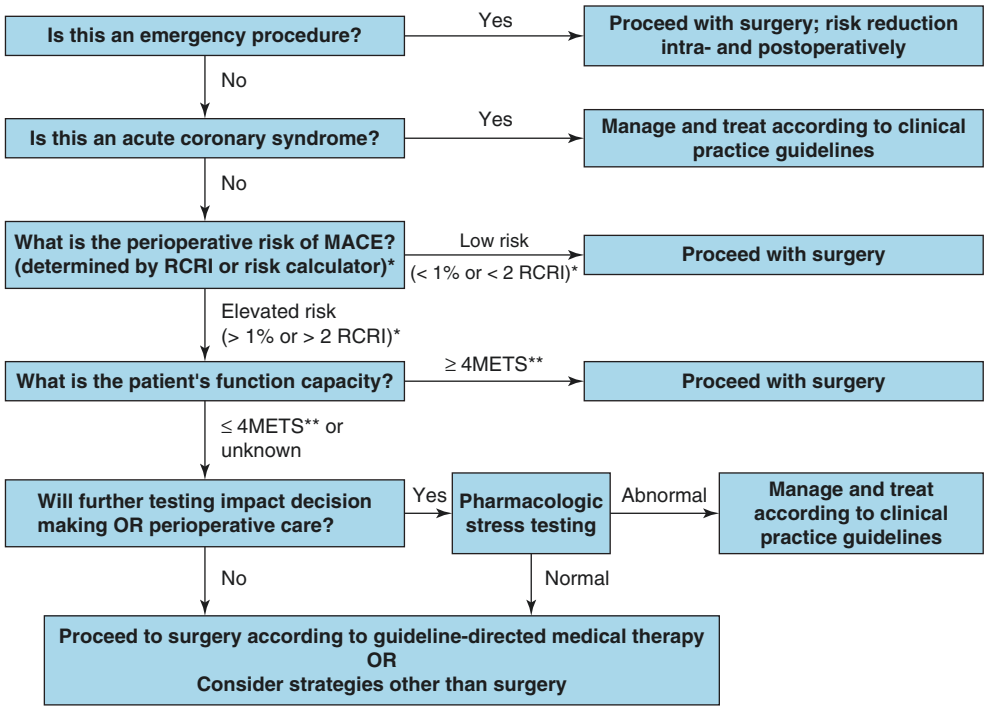

Fig. 9.3 Algorithm to assess the cardiovascular risk of patients for noncardiac surgery

Table 9.3 Revised cardiac risk index

Risk factor	Points
Cerebrovascular disease	1
Congestive heart failure	1
Creatinine level >2.0 mg.dl^{-1}	1
Diabetes mellitus requiring insulin	1
Ischemic cardiac disease	1
Suprainguinal vascular surgery, intrathoracic surgery, or intra-abdominal surgery	1
Risk of major cardiac event	
Percentage risk (95% CI)	**Point totals**
0.4 (0.05–1.5)%	0
0.9 (0.3–2.1)%	1
6.6 (3.9–10.3)%	2
≥11 (5.8–18.4)%	≥3

CI confidence interval

protein (CRP) and brain natriuretic peptide (BNP) are strong, independent predictors of adverse outcomes, and it is advisable to postpone elective surgery until BNP has normalized.

Ischemic heart disease should be evaluated by thorough history taking, review of pertinent data such as previous echocardiography, electrocardiograms (ECGs), cardiac catheterization reports, and a clinical examination. Routine ECG taking is not useful, and clinical risk factors better predict MACE than ECG abnormalities found on preoperative ECGs. Equally, troponin levels detect myocardial ischemia far more reliably than ECGs, which is reflected in part by the fact that MACE presents clinically very differently from ST elevation myocardial infarctions (STEMIs) in that the hallmark signs of chest pain and ST elevations are oftentimes missing. MACE is frequent, silent, and deadly. In the VISION study, a prospective multinational cohort study of patients ages 45 years or older who underwent noncardiac surgery had high-sensitivity troponin T (hs TnT) measurements 6–12 hours after surgery and then daily for 3 days. Postoperative hs TnT values of at least 20 ng/L and an absolute increase of at least 5 ng/L or hs TnT > 65 ng/L were associated with increased 30-day mortality. The VISION study authors recommend obtaining a baseline hs TnT preoperatively in patients in whom postoperative troponin monitoring is planned given the relevance of the absolute change [28]. Patients presenting with cardiac implanted electronic devices are encountered more frequently, and it is expected that more and more patients with advanced heart disease requiring devices such as pacemakers, implantable defibrillators, and resynchronization devices present for noncardiac surgery and more and more complex procedures. Most of the patients will likely be high-risk patients, and a thorough history and physical exam should be taken and clarified when the device was last interrogated, whether the patient depends on its function in order to avoid severe dysrhythmias, particularly bradyarrhythmias or asystole, should intraoperative device malfunction occur. The anticipated electromagnetic interference during surgery should be noted, and a comprehensive perioperative plan should be formulated. Recommendations to interrogate the device are made for pacemakers to occur within 12 months, 6 months for automatic implantable defibrillators, and 3–6 months for resynchronization devices before the anticipated surgical procedure, respectively [29].

Atrial Fibrillation

Atrial fibrillation is the most common arrhythmia associated with a significant increase in morbidity such as heart failure and thromboembolism as well as mortality [30]. Its prevalence increases with age from 0.1% in adults under 55 years to 9% in adults older than 79 years. Men are at higher risk at any age. Hypertension, coronary artery disease, valvular heart disease, heart failure, hypertrophic cardiomyopathies, and congenital heart disease are all risk factors. Hyperthyroidism—including subclinical hyperthyroidism and iatrogenic hyperthyroidism caused by thyroid hormone replacement therapy—has been identified as a risk factor. Last, but not least, mono- and polygenetic inheritance patterns exist, with the latter being more common. Preoperative atrial fibrillation that is new in onset should be evaluated. Echocardiography should be performed, and expert consultation should be sought [31]. Detailed guidelines such as the 2014 guideline for management of patients with atrial fibrillation by the American College of Cardiology [32] with its focused 2019 update [33] exist to aid in the perioperative management of patients with atrial fibrillation presenting for noncardiac surgery, particularly in the perioperative management of anticoagulant therapy.

Pulmonary Conditions and Obstructive Sleep Apnea

Respiratory complications following major, noncardiac surgery are common and increase length of hospital stay, expenditure, and mortality [34]. Preexisting respiratory diseases such as history of smoking, asthma, COPD, or OSA—all thought to be associated with pulmonary complications—are less predictive than a low oxygen saturation or a history of a recent pneumonia before surgery, highlighting that optimization of chronic pulmonary disease will reduce the risk of the patient with COPD, asthma, or emphysema to a comparable level with a patient without these problems [35]. In patients with suspected obstructive sleep apnea (OSA), validated screening tools such as the STOP-Bang questionnaire should be used to identify patients at high risk for OSA and alert the perioperative care team to use strategies to mitigate the risk for postoperative complications. Patients with treated OSA should bring their device and are encouraged to use it. There is little evidence to postpone elective surgery to further workup such as formal sleep studies as long as other medical conditions but especially cardiopulmonary conditions are treated and optimized [36].

Renal Disease

Chronic kidney disease is a highly prevalent, yet underdiagnosed, disease with major implications for perioperative planning. Patients with chronic kidney disease are at risk for acute kidney injury, leading to worsening renal function and progression to chronic renal failure, cardiovascular events, sepsis, and death. Hence, chronic kidney disease should be identified and whenever possible optimized before undergoing major surgery. In a recent review, the authors suggest that patients older than 60 years with diabetes, hypertension, cardiovascular diseases, obesity, autoimmune disorders, or a past medical history of acute kidney injury (AKI) or a family history of chronic kidney disease be screened by determining serum creatinine. The following measures for perioperative preservation of renal function and protection against AKI are recommended: hemodynamic stability by ensuring optimized intravascular volume status and perfusion pressure. Advanced hemodynamic monitoring is required to optimize stroke volume and maintain adequate intravascular volume. Mean arterial pressure (MAP) should be maintained within 20% of the patient's usual pressures and at least 65 mm Hg. Central venous pressure (CVP) should be controlled between 8 mm Hg and 12 mm Hg, and SvO2 should be normal at >70%. Intra-abdominal pressure should be kept at 14 mm Hg or less. Nephrotoxic agents should be discontinued [37]. These measures, while making pathophysiologic sense, are mostly "eminence based" given the lack of reliable and robust data from clinical trials [38].

Coagulation Disorders and Anticoagulant Use

Assessing for the presence of increased risk of bleeding is achieved by a detailed history and physical exam. Routine coagulation studies are not recommended. A decreased platelet count does correlate with perioperative risk of bleeding complications and can be considered. The European Society of Anaesthesiology recently published their updated recommendations for preoperative evaluation of adults undergoing elective noncardiac surgery [39]. Detailed recommendations regarding managing patients on anti-platelet agents and anticoagulant therapy perioperatively can be found there.

Psychological Factors, Chronic Pain, and Opioid Tolerance

Psychological factors such as anxiety, depression, or catastrophizing can impact physical and psychological recovery from surgery [40] and hence should be evaluated and addressed preoperatively. Factors within the domains of mood, attitude, and personality traits are associated either with positive or negative short-term outcomes after surgery. Particularly, anxiety, depression, intramarital hostility, anger, and psychological stress are associated with unfavorable outcomes, whereas self-efficiency, low pain expectations,

optimism, religiousness, anger control, and an external locus of control are protective [41]. Patients with chronic pain and opioid tolerance present unique and complex challenges in the perioperative continuum, not only because of oftentimes being frank opioid dependent but also due to lack of resilience, self-efficacy, and heightened psychological stress and emotional lability. In the new reality of the opioid crisis, health-care providers operate under heightened scrutiny from regulators, government, and law enforcement and urgently require robust perioperative evidence-based pathways for these groups of patients to optimize pain management, minimize adverse outcomes from opioid prescribing, and ensure the best possible functional recovery. Patients with chronic pain, opioid tolerance, and opioid dependence who are contemplated for elective surgery should be evaluated by an experienced team. Preoperative opioid reduction or even cessation should be pursued in conjunction with improving coping skills and psychological resilience. This requires well-organized programs that include counseling and close follow-up [42].

Penicillin Allergy

Penicillin allergies are noted in health records in one of ten patients [43]. The vast majority of these patients, however, does not truly have a penicillin allergy, making the avoidance of this class of drugs unnecessary and, considering potential consequences of using alternatives, even harmful for both the individual patient and population health. Indiscriminate use of broad-spectrum antibiotics increases the risk the occurrence of antimicrobial-resistant organisms as well as infection with *Clostridium difficile* [44]. It is therefore reasonable to refer such patients to formal penicillin allergy skin testing prior to undergoing elective surgery [45].

The Patient Presenting for Emergent Surgery

When time constraints make the optimization of medical conditions in the emergent surgical patient impractical, more weight is placed on enrolling the patient into a comprehensive perioperative pathway to reduce risk for complications and excess mortality and to optimize outcomes. However, even with as little as a few hours, meaningful medical optimization can be achieved by promptly administering antibiotics for sepsis, executing a rational fluid and electrolyte resuscitation plan with early use of targeted vasopressors, and assessing important laboratory data such as lactate, renal function, as well as blood and coagulation studies. Acute anemia from bleeding or coagulopathy should be addressed as early as possible [46].

Conclusion

Preoperative medical optimization complements the concept of the aggregation of marginal gains and is an integral part of enhancing the recovery of surgical patients. Currently, preoperative testing centers are facing a cost versus efficacy dilemma, which can easily be overcome by focusing on patient-specific optimization rather than solely collecting information to minimize day-of-surgery cancelations due to missing data. Close collaboration with surgeons and patients is paramount to assess and optimize patients to improve patient resiliency to surgical stress, enhance their recovery, and enable better survival at higher functional levels. Especially in patient cohorts with full onset of chronic disease such as congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), or chronic pain and patients presenting during complex episodes such as cancer or thromboembolic disease, preoperative medical optimization is expected to provide significant opportunities for improving quality of care and lowering health-care costs. It is paramount that this happens in a collaborative and multidisciplinary fashion.

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Prehabilitation

10

Enrico M. Minnella, Chelsia Gillis, Linda Edgar, and Francesco Carli

Introduction

The goal of enhanced recovery after surgery (ERAS) is to combine many evidence-based perioperative interventions into a coordinated synergistic programmatic approach where each intervention has a little effect when acted individually. Many of the components of the ERAS aim to attenuate the metabolic stress response, such as patient education, carbohydrate drink, early feeding, laparoscopy, and mobilization. When all these interventions are put together, the synergistic approach has a major impact on clinical outcome [1].

Postoperative complications, in particular medical ones, still remain high despite the introduction of ERAS programs, advances in surgical technology, and anesthesia. It might be possible that many of the postoperative complications are related to patient factors. Is it possible that our present patients' preoperative preparation to surgery is not sufficient to mitigate the clinical impact?

While efforts have been made to address any ERAS elements of the intraoperative and immediate postoperative period, the period of time from surgical diagnosis to operation has received modest attention. This interval can be used to optimize patient health and prepare the patient for the postoperative recovery. As patients experience physical fatigue, poor nutrition, disturbed sleep, and decreased capacity to mentally concentrate once they return home from surgery, it would make sense to use the preoperative time in anticipation of surgery to enhance physiological and mental reserve.

Therefore, the process of enhancing functional capacity to enable patients to withstand an incoming stressor can be defined as prehabilitation (Fig. 10.1) [2, 3]. The intent is to implement strategies aimed at minimizing the effect of surgical stress and metabolic deconditioning and to accelerate the return to baseline levels of functional capacity. The postoperative period is not the most opportune time because patients are tired, depressed, and unwilling to engage in any healing process. The term "prehabilitation" counteracts the traditional one of rehabilitation, whereby patients receive interventions after surgery. Conventionally, rehabilitation strategies have focused on the postoperative period as part of the various rehabilitation programs, for instance, arm exercises after breast cancer, strengthening exercises after limb arthroplasty, and aerobic exercises after cardiac surgery.

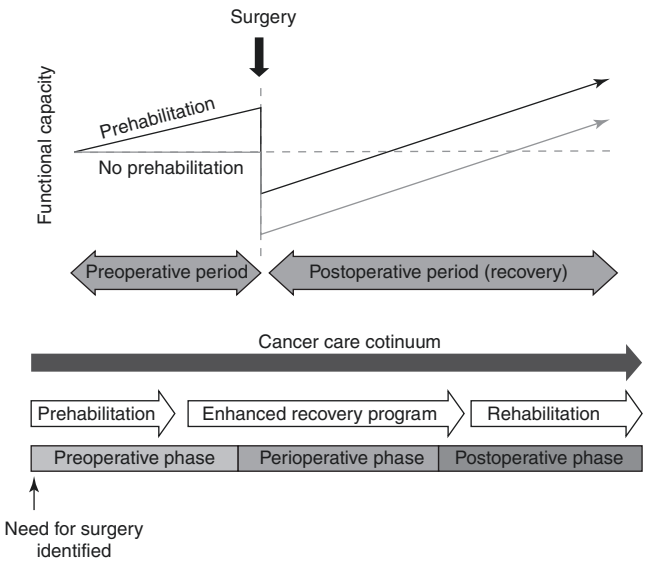

Fig. 10.1 Trajectory of perioperative functional capacity

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With the increase of the elderly frail population, there is a need to focus on restoration of function and increase the physiological reserve. This group of patients, who are more vulnerable to surgical stress, need appropriate evaluation as they are at higher risk of experiencing postoperative complications, thus leading to prolonged hospitalization, disability, and risk of mortality [4]. Prehabilitation can therefore be an attractive strategy for the sedentary individual, the older frail patient, those with comorbidities amenable to treatment, and the patient at nutrition risk and deconditioned.

To optimize organ function in preparation of surgery, it is necessary to assess initially the patient's functional reserve and the specific disease process identified in each organ system. Functional reserve includes physical, nutritional, metabolic, and mental status. In the following sections, assessment of physical activity and risk assessment and stratification will be described. This will be followed by a description of the different components of prehabilitation.

Screening and Assessment

In the attempt to improve the quality of surgical care, the scope of a prehabilitation clinic is not only to reduce the morbidity associated with the surgical intervention but also to promptly restore the patient's level of functioning. Unfortunately, there is no standardized approach, and recommendations, with the intent to provide a guideline-based clinical pathway to optimize patients' functional status before surgery. The first step of this process includes screening and assessment of functional capacity. No single variable accurately and reliably relays the functional status. Mimicking the prethoracotomy assessment of the respiratory function [5], we propose a "three-legged stool" management of functional capacity, focusing on physical, nutritional, and psychological status (Fig. 10.2). This model aims to catch the complexity of the functional capacity and to enable the clinician to selectively intervene on each risk factor, if present, and personalize the therapy. This approach is driven by evidence-based practice, acknowledging the lack of large, conclusive, randomized trials in this setting [6]. While waiting for new clinical studies, our evidence-based practice stands on international guidelines [7–11] and relies on the strong rational underpinning of the synergistic effect of exercise, nutrition, and mental health. For this chapter, we discuss a model that could be applied to elective, major, abdominal cancer surgery. This pathway should be fully integrated into a standard, comprehensive patient management, encompassing elements of usual preoperative care, such as medication management, perioperative blood management, and smoking cessation (elsewhere treated in the book).

Considering the high prevalence and the impact of functional deconditioning [4, 12], all patients should be screened.

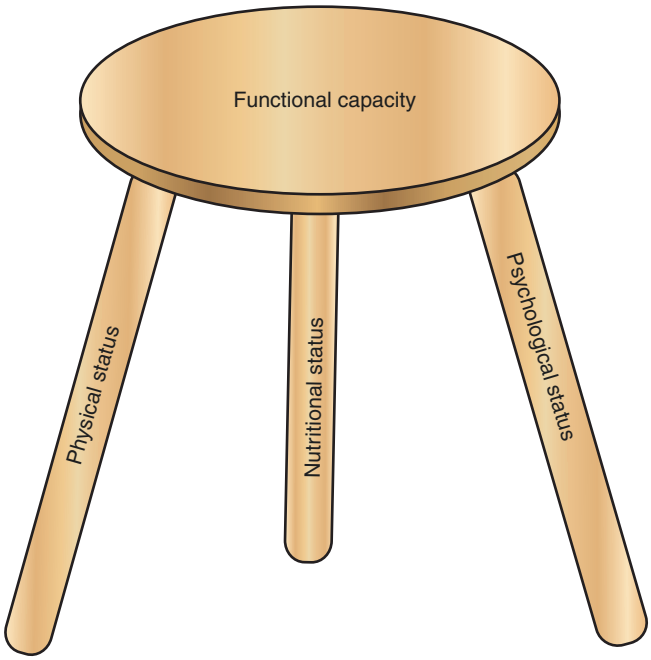

Fig. 10.2 Management of functional capacity

Figure 10.3 shows how screening identifies factors associated with increased risk for specific impairment of patients' functioning level [13–17]. The process is designed to be safe, quick, easy to administer, and cost-effective. Thus, a complete history and physical examination and self-reported measures are the first-line approach. Several elements of the medical history are of notable importance, such as chronic disease (e.g., cardiorespiratory disease and diabetes for, respectively, physical and dietary management), infection, recent hospitalization, and prior abdominal surgery. Random laboratory and instrumental testing with low predictive value that lacks specific workup or treatment should not be performed. Once identified, high-risk patients could further proceed to the assessment phase through selective workup. It is a time- and resource-consuming process that requires expert healthcare providers and should involve only high-risk population. Once assessed and diagnosed, exercise intolerance, malnutrition, and psychological distress should be the target of selective and personalized intervention.

Nutritional status is frequently impaired in surgical population [18]. Clinical signs, anthropometric data, and physical examination are imperative to detect nutrition imbalance, in form of both undernutrition and overnutrition [19]. Weight loss is one of the most validated parameter and could reflect both the degree of inflammation and the underlying disease. An important risk factor is a loss of 10% over the preceding 6 months, or more than 5% in 3 months. Elements of interest are signs of loss of muscle mass and subcutaneous fat and localized or generalized fluid accumulation that may also mask weight loss. Handgrip strength is simple to detect, and

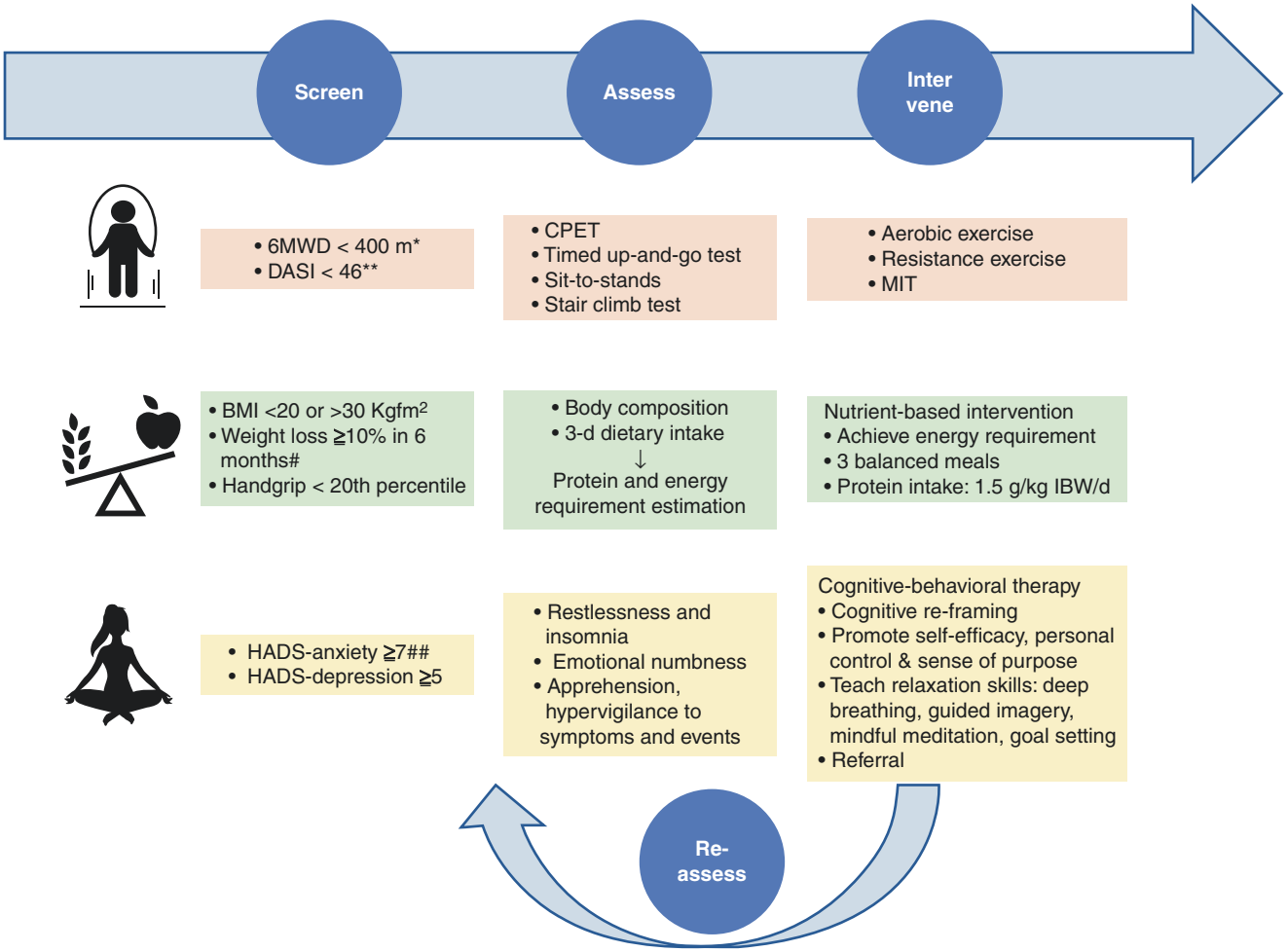

Fig. 10.3 Proposed clinical pathway for preoperative functional optimization of patients undergoing major abdominal cancer surgery. (Adapted from Minnella and Carli [13]). 6MWD 6-min walking distance, BMI body mass index, CPET cardiopulmonary exercise testing, HADS Hospital Anxiety and Depression Scale questionnaire, Anxiety and Depression sub-scale, IBW ideal body weight, METs metabolic equivalents, NRS-2002 Nutrition Risk Screening 2002. *Brunelli [14]; Minnella [15]. ** Struthers [16]. # or ≧ 5% in 3 months; ##Singer[17]

it is a reliable index of functional and nutritional status [20]. For a more standardized and accurate practice, we suggest using validated clinical tools that include both history and physical examination findings, such as the Nutritional Risk Screening tool (NRS 2002) [21] and the scored Patient-Generated Subjective Global Assessment (PG-SGA) [22]. Laboratory data should be interpreted with caution since markers of catabolic state, such as albumin, prealbumin, and transferrin, reflect severity of inflammation rather than nutritional status. Electrolytes, glucose, and creatinine are useful to guide both screening and intervention. Once the risk of under- or overnutrition has been established, a more detailed assessment should be performed by a dietitian. Current nutrient and caloric intake may be obtained from a 3-day recall diary; medications, specific symptoms, food allergies and intolerances, and dietary restrictions may be investigated, and body composition may be assessed. All these elements are required to determine energy requirement, identify inadequate dietary intake, and provide a correct nutritional intervention. Indirect calorimetry is considered the gold standard method for establishing energy expenditure; nonetheless, commonly used predictive equations, such as Harris-Benedict equation corrected for the metabolic stress related to surgery and cancer, may be considered a valid alternative in ambulatory setting.

Low exercise capacity is a prevalent condition with significant implications for patients undergoing surgery [23, 24]. The 6-min walk test (6MWT) is a cost-effective submaximal exercise test and a well-validated index of functional status and response to medical and surgical interventions in a wide variety of patient groups. It measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 min [25]. Although 6MWT alone is not a comprehensive test of functional capacity, it is a sensitive surrogate to evaluate physical fitness, and, for practical reasons, it is considered as a good screening tool. A total

distance walked during 6 min below 400 meters may be considered a sign of low physical fitness [15]. Patients identified as high-risk population should undergo a complete assessment of physical status, performed by a trained specialist with experience in cancer care. Both aerobic and strength may be included. The cardiopulmonary exercise testing (CPET) is the gold standard for assessing functional capacity [26]. It is an integrative, objective, and dynamic test involving respiratory flow and gas exchange analysis that measures oxygen consumption in response to the stress of progressive exercise. CPET has several clinical applications in a preoperative setting beyond the evaluation of exercise capacity, such as identification of the causes of exercise intolerance, evaluation of surgical risk and prognostic outcome, detection of exercise-induced adverse event, exercise prescription, and response to prehabilitation or preoperative exercise. Thus, once again, the role of screening and assessment does not only provide a static picture of the patient but shall aim to guide a safe, purposive, personalized, impairment-driven intervention. The next paragraphs will explore the main areas constituting multimodal prehabilitation: exercise, nutrition therapy, and coping anxiety techniques.

Psychosocial distress is often overlooked in perioperative medicine, and routine screening for anxiety and depression is rare [27]. Mental health should be assessed in all cancer patients, and, thus, all health professionals involved in cancer care should be aware of the basic elements of screening and referral. A simple and validated tool for screening is the Hospital Anxiety And Depression Scale (HADS) questionnaire [28]. In literature, several cutoffs have been proposed, and there is still a lack of consensus. Once identified, patients at risk should undergo a psychosocial intervention, and patient with moderate to severe depression or anxiety should be referred to a psychiatric service.

Elements of Intervention

The purpose of the baseline assessment is to determine the fitness status and predict the risk associated with surgery and postoperative recovery. A more comprehensive approach includes evaluating treatment options, formulating recommendations, and articulating the benefits and risks to patients. In the context of prehabilitation, the baseline assessment can guide the clinician on how to optimize patient fitness in anticipation of surgery with the aim to minimize the rate of complications and accelerate the recovery process.

The various elements which characterize the prehabilitation program, nutrition supplementation, endurance and muscle strengthening, relaxation, and empowerment via education, need to be integrated in enhancing patients' physiological and metabolic reserve. Clearly the prehabilitation program is not a "one size fits all" program but rather involves generalized concepts of fitness together with specific individualized assessments and interventions, where safety plays a major role. Although much of the early cancer prehabilitation literature focused on exercise training as a single intervention modality [29], there is strong realization from recent reports that other modalities such as nutritional and psychological interventions either alone or in combination with physical activity have a significant impact on functional outcome [30]. This expanding scope of prehabilitation is likely due to the acknowledgment that non-exercise interventions may also be beneficial but must be integrated with other components in order to achieve greater effect. It has to be said that prescribing intense exercise training as a single modality may actually be detrimental to some patients who lack physiologic reserves. This is true for frail elderly patients who often present with decreased muscle mass and low protein reserves [31]. These patients may in fact be unable to tolerate an increase in exercise before surgery without sufficient anabolic substrate based on adequate energy and protein supplementation.

Individual elements of the prehabilitation program are made more effective if integrated with the preoperative components of the ERAS program. For example, better glycemic control can be achieved if hypoglycemic agents are used in conjunction with exercise training and appropriate nutritional intervention. Similarly, a more efficient impact of exercise can be achieved if anemia is sufficiently corrected.

It would then make sense if the hospital prehabilitation program is made available to the surgical patient starting at the time the surgeon decides with the patient the need for surgery. This program can be then integrated in the preoperative clinic. Regular evaluations of how these interventions impact on patient's functional capacity provide the necessary information which remain essential for the development of subsequent therapeutic strategies. The prehabilitation unit's multidisciplinary group includes anesthesiologists, internists, surgeons, nurses, physiotherapists, kinesiologists, nutritionists, and psychologists, all working together to promote cost-effective use of resources at all levels through a patient-centered care delivery model. A well-functioning prehabilitation unit works closely with the preoperative clinic and can be effective in reducing preoperative testing and unnecessary consultations, reducing surgery cancellations, and improving coordinated care and development of pathways where the patient is at the center of care. This fits within the scope of ERAS and can promote better outcome.

Role of Exercise

Physical inactivity is a leading determinant of global morbidity and mortality [32]. Recently, exercise and physical activity have become a key strategy not only for primary

prevention but also for counteracting the adverse effect of cancer and its treatment [33, 34]. There is an urgent need to implement exercise in perioperative phase of major oncologic surgery, since several guidelines and position statements already recommend its integration as a standard practice in cancer care [7, 35, 36]. Physical activity is any sustained body movement that increases energy expenditure, whereas exercise is planned, purposeful, and repeated activity, aimed to improve or maintain health and fitness [37].

Training should be prescribed, delivered, and monitored by a certified specialist with proper training in cancer care, such as kinesiologist, physiotherapist, clinical exercise physiologist, or a physician. Any unstable or acute cardiorespiratory condition constitutes a contraindication to exercise [38]. The main targets of a prehabilitation program are (1) aerobic capacity, (2) muscle strength and endurance, and (3) daily physical activity (see Table 10.1). Aerobic exercise, the cornerstone intervention for increasing cardiopulmonary fitness, involves large muscle groups using oxygen-supplied energy [39]. The duration of the exercise is dependent upon the intensity of the activity, but each session should be of 10 min duration at least. Running, brisk walking, cycling, and swimming are common and effective modalities. For aerobic training prescription, CPET provides the most accurate quantification of functional capacity and a comprehensive evaluation of the integrative respiratory, cardiovascular, and muscle response to exercise. Furthermore, CPET detects potential exertional symptoms or adverse events, such as inducible ischemia, allowing a safe prescription. Strength training, implying the muscles to work or hold against an applied force or weigh, is another key component of the program. Muscle fatigue, defined as a decline in force or power production in response to contractile activity, is a common adverse effect of surgery [40]. The impaired muscle function and structure occurring after surgery is related to stress response, limited mobilization, poor food intake, and impaired aerobic capacity. Reduced joint mobility can occur in the absence of disease in older adult, and any impairment could lead to activity limitation. Stretching and strengthening exercise and warm-up and cool-down activities should always be performed in a training session. Moreover, patients with poor mobility should perform physical activity 3 or more days per week to enhance balance and prevent falls [39].

Cancer site-specific training, exercise for patients with disabilities, behavioral change motivation, sport/activity choice, safety of training, and specific element of exercise prescription such as module, duration, intensity, pattern, frequency, and progression are central elements, but a detailed description goes beyond the purpose of this chapter. Preoperative training may conform to the guideline provided by the American Heart Association (AHA), the American College of Sports Medicine (ACSM), and the recommendations on physical activity of the World Health Organization (WHO) [32, 41, 42]. Thus, patients aged 65 years and above are advised to:

- Perform at least 150 min of moderate-intensity aerobic activity per week, or 75 min of vigorous-intensity aerobic physical activity per week
- Perform a resistance exercise involving major muscle groups, at least 2 days per week
- Minimize sedentary behavior

Table 10.1 Example of different components of exercise training in the context of a prehabilitation program

	Frequency	Exercise	Duration	Intensity
Warm-up	Before every training	Deep breathing, posture, range-of-motion exercises Cardiovascular-specific warm-up	10 min	HR: 40–59% RPE: 12–13 VO_2AT: 80–85%
Aerobic training	3/week	High-intensity interval training Walking (moderate speed/grade) Bicycling Running Swimming	20–25 min	HRR: 80–89% RPE: 16–17 VO_2peak: 80–85%
Resistance training	2–3/week	8–10 reps per set, 1 min rest between sets, 3 sets per exercise Lower body: leg press, hamstring curl, lunges Chest and Core body: sit-ups (abdominal crunches), bench press, push-ups or modified push-ups Upper body: biceps curls, triceps extension, front deltoid, military press, upright seated row.	30 min	50–69% 1-RM 12–13 RPE
Flexibility	After every training	15–30 sec per repetition Stretching and strengthening exercise	5–10 min	
Cool down	After every training	Cardiovascular-specific cool down	5 min	

HRR heart rate reserve, *RPE* rating of perceived exertion (6–20 Borg scale), *1RM* one repetition maximum, VO_2 oxygen uptake (measured with cardiopulmonary exercise testing)

Role of Nutrition

The nutrition component of a multimodal prehabilitation intervention is designed to meet individual nutrient needs and lifestyles, as well as work synergistically with the exercise component to support gains in lean mass before and after surgery. For the surgical patient, there are several "opportunities" in which nutritional status could be compromised [43]. The onset of disease and disease-treatments, such as anticancer therapies, might introduce metabolic abnormalities, including inflammation, that alter nutrient needs [44]. As an example, there are several amino acids that may become "conditionally" essential in inflammatory states [45, 46]. Biosynthesis of the acute phase proteins associated with inflammation imposes a new demand for aromatic and sulfur amino acids [45]. A stable isotope investigation estimated that in pancreatic cancer patients experiencing an ongoing inflammatory response, 2.6 g of muscle protein would need to be catabolized to support synthesis of 1 g of the positive acute phase reactant fibrinogen, if food was not consumed [46]. Dietary intake must compensate for metabolic demands; otherwise lean tissues, including skeletal muscle mass, are catabolized.

Patients, however, might find it difficult to meet their nutrient needs through food intake because of mechanical obstructions (e.g., tumor-related obstructions); gastrointestinal abnormalities, such as malabsorption (e.g., diarrhea); and the onset of several nutrition-impact symptoms (e.g., loss of appetite) related to disease and its associated treatments [44]. Patient-related factors, including social isolation and socioeconomic status, additionally impact food intake [47]. Yet, before and after surgery, malnutrition risk and malnutrition (an *unbalanced nutritional state* that leads to *alterations in body composition* and diminished function [48]) often go undiagnosed. As a result, patients face the surgical stress response in a suboptimal nutritional state with diminished physiological reserves [49, 50] to respond to the demands of the impending surgical stress response [51]. Malnourished hospitalized and surgical patients have significantly worse clinical outcomes, including mortality [52–55], greater odds of complications [52, 56–59], more frequent readmissions [52, 54, 60, 61], longer hospital stays [52, 54, 56, 59, 60], and increased healthcare costs [52, 62]. Additionally, two large multivariable analyses of preoperative computed tomography-defined body composition in colorectal cancer patients identified that low muscle mass (i.e., sarcopenia) is an independent predictor of overall survival [63], the presence of myosteatosis (fatty infiltration in muscle, thought to be an indicator of muscle quality) is associated with prolonged hospital stay [63, 64], and patients with visceral obesity, particularly obese patients with low muscle mass (i.e., sarcopenic obesity) [64], were more likely to suffer from 30-day morbidity, including hospital readmission [63]. Post-surgery, patients are subject to several additional nutritional barriers, including the surgical stress response and organizational barriers in hospital (e.g., missed meals for clinical investigation). As an example, insulin resistance is a typical consequence of the surgical stress response that has been observed to last for weeks even after uncomplicated surgery [51, 65]. Insulin resistance disrupts normal metabolism; the incapacity of insulin to facilitate the uptake of glucose into cells (i.e., insulin resistance) exaggerates catabolism (glucogenic amino acids are directed toward fuel pathways rather than anabolic pathways) [51]. Food intake, again, must offset the consequent catabolism of injury in order to attenuate losses in lean mass. Patients, however, do not achieve adequate intake in hospital. The Canadian Malnutrition Task Force (CMTF), a prospective study involving 18 acute care hospitals across Canada, identified that nearly 50% of hospitalized patients felt "too sick" to eat, a third of patients had difficulty opening food packages, two-thirds were not given hospital food when meals were missed, and nearly half did not get help when needed [66]. Even patients receiving standardized ERAS care do not meet minimally adequate requirements for protein [67, 68] and require nutrition education to correct misconceptions that impede adequate intake in hospital [69]. Finally, patients are often discharged home without nutrition follow-up, and they suffer further nutrition-impact symptoms from their pain medications and/or require additional treatments, all the while, relying on their own knowledge of food and nutrition to begin the process of convalescence [70–73]. After careful consideration of the patients' surgical care trajectory, it is evident that if the best patient outcomes are to be realized, nutrition management must begin preoperatively to optimize nutritional status in preparation of a nutritionally compromising surgical journey [11, 51].

Body proteins are constantly synthesized and degraded to maintain a neutral whole-body protein balance in normal, healthy adults [74]. The extent to which body proteins are degraded for reuse is considerable; however, this recycling is not 100% efficient, and the essential amino acids cannot be synthesized de novo, necessitating a daily requirement to ingest dietary protein [74]. When protein ingestion from food does not meet metabolic demands, body tissue is *catabolized* to meet needs. By meeting metabolic demands and maintaining homeostasis, largely through food intake, serious catabolism and losses of body protein and strength are avoided. When whole-body protein synthesis outweighs protein breakdown, *anabolism* is favored [74].

Prehabilitated patients achieve anabolism and thus maintain and/or build lean mass before surgery through adequate intake from food, through use of protein supplements, and by performing regular resistance exercise [75]. Dietary protein consumption and resistance exercise training exert independent and additive anabolic effects [74]. After

ingestion of protein without exercise, a transient increase in the blood circulation of amino acids promotes muscle protein synthesis [76]; in healthy individuals, this anabolic effect is offset by daily periods of catabolism (i.e., fasting between meals and during sleep) to produce an overall whole-body neutral protein balance that maintains lean mass [74]. Resistance exercise without food intake also stimulates muscle protein synthesis [74, 77]. However, resistance exercise also elicits a concomitant increase in muscle protein breakdown [77]. The net effect is that muscle protein balance improves (i.e., becomes less negative so fasted-state losses are less) after exercise, but does not become positive in the fasted state [74]. Still, without a positive net protein balance, a state in which protein synthesis exceeds protein breakdown, lean tissue accretion will not occur. Intuitively this makes sense: building lean mass requires the synthesis of new proteins, and dietary amino acids, referred to as "the building blocks of protein," are the substrates [74]. Stable isotope studies have confirmed that the net muscle protein balance post-exercise remains negative until amino acids are available [74, 77, 78]. It is thus the synergistic effect of feeding and exercise that promotes a positive protein balance in muscle. Repeated bouts of resistance exercise and protein feeding stimulate gains in lean mass [74, 75].

Role of Psychology

There is compelling evidence that psychological stress influences functional and emotional capacity and that psychosocial interventions implemented before surgery can minimize that stress [79]. Preoperative preparation is an opportunity to reduce stress by reinforcing and developing three psychological constructs important for health, physical activity, and well-being: self-efficacy, a sense of purpose, and personal control.

Self-Efficacy

Is self-efficacy a major determinant in human behavior? Can self-efficacy in patients be developed by healthcare practitioners? Do successful exercise programs depend on self-efficacy?

The response to the above questions is yes.

The term was first used and developed by Albert Bandura. He defined it as, "the belief in one's capabilities to organize and execute the courses of action required to produce given attainments" [80]. One's beliefs about one's capabilities to accomplish something have a profound effect on one's success. Ability is not a fixed property; there is a great deal of variability in how people perform tasks, how they succeed at different time periods, and how ability varies according to the task at hand. We learn to have a general sense of self-efficacy in childhood and continue to develop it throughout our lives particularly as it changes with different circumstances. Self-efficacy differs from the many other concepts in social psychology concerning the human psyche, such as self-esteem and self-confidence. Self-efficacy focuses on "doing" rather than on "being" [80].

There is a substantial body of research on the positive role played by self-efficacy in exercise [81]. It has been shown to be a reliable predictor of the adoption and maintenance of physical activity in healthy adults [82]. There is also convincing research evidence that self-efficacy moderates the effects of interventions on objectively measured physical activity independent of other personality characteristics. Believing that a better fitness level helps in recovery postoperatively leads to an improvement in one's functional ability even given likely constraints and challenges to exercise.

Sense of Purpose

Having a sense of purpose is the motivation that drives one to fulfillment through achievement of a task or goal. It is an anticipation outcome that is intended to guide planned actions. The importance of having a sense of purpose gained attention with the rise of positive psychology which is defined as the scientific study of what makes life worth living [83].

A sense of purpose in life is a modifiable factor and, thus, a fitting focal point in preoperative interventions. Theoretically, participants in a prehabilitation program have a sense of purpose by default as they chose to prepare themselves for upcoming surgery. Acknowledging and strengthening that sense of purpose is thought to contribute to better surgical outcomes. There is a robust link between negative psychosocial risk factors and adverse health outcomes and conversely between positive psychosocial factors and positive physical and physiological functioning [84]. A sense of purpose may play an especially important role in maintaining physical function among older adults [85].

Personal Control

Personal control is the extent to which people perceive control over their environment rather than feeling helpless. It is a fundamental psychological resource and a powerful influence on well-being throughout life. In preparing for surgery, it is imperative that people realize that they are responsible for several pre- and postoperative activities; deep breathing, relaxation, physical activity, and nutrition. There is a large body of research linking a sense of personal control, healthy behaviors, and good psychosocial functioning [86].

How We Integrate the Above Concepts; Guidelines from the Prehabilitation Platform

Even though almost half of the participants self-report little or no anxiety or depression, the majority are receptive to dialogue and discuss helpful psychosocial strategies prior to surgery. Most patients accepting the prehabilitation program take part in either 1 or 2 hourly sessions a few weeks before surgery. Patients who require more assistance may be seen more often or referred to a mental health practitioner as needed.

Fostering a sense of self-efficacy, purpose, and personal control is embedded in the goals of the intervention. Given that the time for psychosocial interventions is limited, we can merely introduce good coping strategies, individualize them according to participants' expressed needs and values, and stress that practice will bring noticeable results. We begin by asking what they would like to get from the program, to describe themselves and their family support, and to discuss their interests and values. We inquire whether the patient is anxious, worried, or stressed about the current situation by starting a conversation about what matters to them and their goals regarding their upcoming surgery. We can highlight and support their goals by acknowledging their strengths and emphasizing past and present positive experiences. We overtly link the practice of exercise and good health with a rise in self-efficacy, personal control, and sense of purpose.

We highlight the importance of practicing some form of relaxation. Relaxation is framed as a useful tool for their personal use, aiding them to achieve a state of well-being and a sense of personal control. Methods of relaxation include deep breathing, progressive muscle relaxation, guided imagery, mindful meditation, body scanning, and focused attention in the present. We model a form of relaxation training that appears acceptable to the patient and which includes being aware of one's breath. We also demonstrate deep breathing and encourage practice by having the patient model our technique. All participants are offered a CD on relaxation.

To explain the concept of personal control, we discuss how the brain works, moving from encountering facts (over which there is little or no control) to the thoughts which then arise (and over which we have total control), leading to an emotional response which is readily apparent. This practical explanation seems to be understandable and helps strengthen the patient's sense of self-efficacy and control over how he/she copes with the upcoming surgery. We provide a simple diagram linking facts, thoughts, and feelings as a visual reminder.

A systematic review identified behavior change techniques that link self-efficacy to improved physical activity [87]. We incorporate them throughout the session by pointing out experiences where they have or had performed a task successfully and attained a sense of mastery using their skills.

We encourage the use of social modeling by inviting participants to observe how similar people succeed in similar situations through sustained effort, either through face-to-face interactions, via the Internet and other social media, or through literature. Positive psychology interventions have delineated various areas where a sense of purpose can be cultivated. We have chosen a strengths-based approach where we help the participants recognize their strengths by discussing and acknowledging their internal and external values and resources both past and present.

In summary, self-efficacy, a sense of purpose, and a sense of personal control are emerging as strong and independent contributors to good health and exercise. They are basic human attributes that can be fostered by means of simple, straightforward techniques available to healthcare practitioners. Participants leave the session(s) with the following tools: a familiarity with relaxation and deep breathing, knowing the power of their thoughts, and the realization that they have a sense of purpose. We conclude with the notion that practicing those tools is all important and increases the likelihood of a successful surgical outcome and prepare them for future impairments if they occur.

Effective Prehabilitation

As we have seen in the previous sections, a detailed evaluation of a patient's physiological reserve is followed by a structured, personalized prehabilitation program that takes into consideration the type of surgery, the patient's current health status, and state of the disease. The implementation of such a program needs to be followed by posttreatment surveillance. In the cancer prehabilitation conceptual model, anticipation of future impairments is a necessary step to determine the effectiveness of the interventions. This type of monitoring is particularly valuable in patients with several comorbidities and those with limited functional capacity.

The questions often raised by clinicians and administrators are about cost-effectiveness of the prehabilitation program. It would make sense to target a population who could benefit most from either unimodal or multimodal interventions with the intent to obtain better functional capacity and clinical outcome at a reasonable cost for the health service [15]. The preoperative clinic can be the site where patients with multiple comorbidities or with low functional capacity can be identified and referred to the prehabilitation unit for screening, assessment, and finally therapeutic prescription. This requires close integration among the various disciplines and the formulation of an interventional pathway which initiates at the time of the diagnosis, continues throughout the

perioperative trajectory, and follows patient during the continuum of care once they are discharged home. The multidisciplinary team could meet regularly to review and discuss high-risk cases. This same team could collaboratively create a treatment plan that balances the advantages and disadvantages of surgical and nonsurgical approaches to disease management and is anchored in the patient's values and goals.

Data from reviewing the literature on surgical prehabilitation have identified the potential impact on functional capacity before and after surgery. Besides, preliminary work on the effect of preoperative multimodal preconditioning on surgical outcome has shown fewer medical complications and decreased length of hospital stay [88, 89].

There has been a proposal for patients undergoing surgery that surgical homes, which are analogous to the medical homes, might be the future way to provide multimodal care. Before a high-risk patient entered the surgical home for treatment, an overall management plan would be discussed by a multidisciplinary team, like the tumor board review that is now used in oncology.

Conclusion

Surgical prehabilitation is an emerging concept which complements the innovations in perisurgical care and technology following the introduction of fast-track and ERAS programs. There is a strong realization that postoperative outcome depends upon perioperative factors and patient health and functional status, being the last factors modifiable. With an increasing aging population and lowering surgical mortality, patients are concerned with their quality of life, cognitive well-being, and community reintegration. In this context, a prehabilitation program integrated in the perisurgical care makes sense and needs to receive more attention.

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Cognitive Behavior Counseling: Preoperative Preparation in ERAS

11

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Introduction

Preoperative anxiety and lower self-efficacy are often associated with poor surgical outcomes. Although preoperative counseling is considered to be an essential element of enhanced recovery after surgery (ERAS), there is little evidence to indicate the application of formal behavioral therapy, such as cognitive behavioral therapy (CBT), which has been widely utilized in a wide variety of healthcare disciplines. CBT is based on the assumption that our thoughts affect our emotions and behaviors, and it aims to change and overcome negative thoughts and feelings by developing coping mechanisms, which are best suited in ERAS. Effective CBT should include a collaborative approach, where patients utilize their own experiences effectively to define and manage their problems. Mutually agreed-upon realistic goals also underpin the success of CBT.

Cognitive Behavioral Therapy

In the context of preoperative preparation, preoperative counseling is an essential element of an ERAS pathway [1]. This is not only important to prepare patients for surgery but to help them overcome their fear and anxiety about their condition, as well as recovery. Many patients undergo surgery for cancer, and the information provided regarding the newly diagnosed disease can be overwhelming to the extent that any additional information that is related to ERAS may lead to cognitive overload and ultimately lack of compliance. There is compelling evidence that stress can influence functional and emotional capacity and that preoperative interventions can minimize that stress [2, 3].

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The concept of CBT has been adopted within health services to help patients overcome overwhelming problems by breaking them down into smaller parts. This therapy has been successfully practiced in a number of disciplines [4], and it includes controlling situations, thoughts, emotions, physical feelings, and actions, which are all interconnected within the context of recovery after surgery. In preoperative settings, these patients may suffer from anxiety related to their diagnosis/prognosis as well as physical pain because of the condition and subsequent surgery. This may lead them to suffer in silence or not be able to cope with their symptoms, either because of the disease or the therapy. It is challenging to separate these components, but reassurance remains a fundamental part of enhanced recovery, no matter how advanced the disease, to ensure that the multidisciplinary team is there to support patients throughout their whole journey. It may be argued that within the financial constraints of healthcare services, a trained psychologist may not be available to routinely provide this treatment. However, the basic principles of CBT have become an integral part of most healthcare professionals' skills when dealing with surgical and cancer patients; and often the role is fulfilled by an ERAS facilitator, who can play an important role in helping patients overcome the negative feelings and improve the way they feel.

An essential component of prehabilitation is cognitive behavioral changes to enhance the compliance with the intervention. Preoperative anxiety and lower self-efficacy are associated with poor surgical outcomes. Therefore, it is important for prehabilitation programs to place the onus on an individual, in order to engage in healthy behaviors, thus giving them a high sense of control over their own health by developing self-efficacy. This refers to the individual's perceived belief to cope effectively with upcoming situations and problems [4]. Self-efficacy is learned in childhood, developed throughout our lives, and is a major determinant in human behavior [5]. It hugely influences an individual's beliefs, confidence, and capabilities and may determine how they behave or react to situations [5, 6].

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Many studies have indicated that patients with higher self-efficacy levels would be more likely to confidently engage in the necessary behaviors, such as exercise and diet, in order to enhance their health [7–9].

CBT addresses an individual's perception and thoughts surrounding their current issues, rather than focusing on past problems and experiences. It helps patients to reappraise their negative thoughts and develop coping strategies to overcome their fears and anxieties.

Integration of CBT Within Prehabilitation Programs

The concept of preoperative optimization has nowadays been expanded to encompass physiological, psychological, and emotional wellbeing within the context of the prehabilitation pathway [10].

In a randomized control trial, conducted by Carli in 2014 [11], a coping strategy to reduce anxiety formed one of a three-armed intervention (in addition to nutritional and physical exercises). Relaxation therapy was used by a trained psychologist, based on imagery and visualization coupled with breathing exercises. The trimodal program led to improved functional activities following colorectal cancer surgery. This has particular relevance to elderly and frail patients who are physically and biologically deconditioned and in whom preoperative counseling programs could be essential to enhance the compliance with physical and nutritional elements of prehabilitation [10].

Multimodal prehabilitation may also include strategies for smoking and alcohol cessation prior to surgery [12].

CBT is a well-practiced therapy in smoking and alcohol cessation, as it combines changing and restructuring thought processes with new learning behaviors. Further details on counseling for smoking and alcohol cessation are provided in Chap. 8, but in brief, a collaborative approach between primary and secondary care is fundamental to allow sufficient time for the intervention to demonstrate success before surgery.

CBT can be conducted in the community, at hospitals, or at the patient's home, based on logistics and resources in the healthcare system, but an effective CBT should include:

- *Collaboration*

Ultimately, teaching patients to be their own therapist by helping them to understand their current ways of thinking and behaving could be an effective tool that can support their diagnosis and treatment.

The key elements of CBT may be grouped into those that help foster an environment of collaboration between the wider concept of the multidisciplinary team, including primary care, to support the structure and problem-oriented focus of CBT.

A collaborative approach is based on empiricisms [13] in which collaborative relationships between therapist and patient, as well as the whole team, may identify maladaptive cognitions and behaviors. Additional nonspecific elements are also required for a successful collaborative approach. These include empathy, understanding, rapport, and authenticity. A healthcare worker needs to explain the rationale of the CBT and utilize patients' own experience to help them effectively define their problems and gain skills in managing them [14].

- *A SMART Approach*

The second key element of CBT is a problem-oriented approach, which includes mutually agreed-upon goal setting that is specific, measurable, achievable, realistic, and time related (SMART) [15]. For example, a goal for patient mobilization after hip or knee surgery will differ from patients undergoing colorectal resections. The same is true for oral intake for both groups of patients, for instance. It is our task as healthcare professionals to identify realistic initial goals for a patient to focus their recovery on, which are directed toward the patients' current feelings prior to surgery. Providing patients with a large number of tasks that seem equally important can be confusing and less productive. There may be a need to identify one or two tasks for patients to focus their energy and mind to achieve in the immediate recovery period. These may be different for recovery after discharge.

- *Structured and Time-Limited*

CBT should be structured and time-limited treatment within the concept of recovery, as this may help the patient focus their mind to achieve it in the postoperative recovery period. This is related to the previous point (task specific), and this could be the distinction between CBT and mindfulness within this context. Mindfulness refers to the awareness that can be developed through paying purposeful attention to the present moment and non-judgmentally observing the minute-to-minute experience [16]. The concept suggests that accepting the present can lead to a reduction in psychological distress by developing better interpersonal relationships [17].

Key Points

- Patient emotions toward recovery are influenced by their perception of their illnesses and surgery.
- Patient counseling is an integral part of ERAS to reduce their anxiety prior to surgery.
- CBT can be an effective instrument in changing patient behavior toward their long-term health patterns and habits.
- Within prehabilitation, patient counseling to address their emotional needs and self-efficacy is an integral part to enhance compliance with multimodal interventions to improve their whole wellbeing prior to surgery.
- CBT should involve a collaborative approach that is problem-oriented and time-limited that is directed toward recovery. This drives effectiveness of CBT within ERAS.

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Bowel Preparation: Always, Sometimes, Never?

12

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Introduction

The administration of bowel preparation prior to elective colorectal resection is contentious. There is dogma and strongly held opinion both for and against. At present there is a cultural divide between the USA and many countries in Europe, particularly regarding guidelines and recommendations in this area advocated by the Enhanced Recovery After Surgery (ERAS®) Society and the American Society for Enhanced Recovery (ASER) [1–3]. This chapter tries to address the evidence that exists with regard to benefits or otherwise of mechanical bowel preparation (MBP) alone or MBP combined with oral antibiotics in different circumstances and in the context of ERAS.

The original work on what has come to be known as "enhanced recovery after surgery" (ERAS) was in the field of colorectal surgery [4], and this remains the area in which the most research evidence exists. One of the dogmas of colorectal surgery has been the necessity to administer mechanical bowel preparation for patients undergoing colorectal resection, and this is an element of treatment that has been challenged in the context of ERAS. Its avoidance has been a central tenet of colorectal ERAS since its inception.

Bowel preparation was first established during an era of open surgery, limited antibiotics, and sutured anastomoses, which necessitated opening the bowel within the abdominal cavity. Modern colorectal surgery with its emphasis on laparoscopy and the use of stapling technologies avoids this in most circumstances, and so it is possible that the rationale for bowel preparation is no longer valid. Indeed it has been shown in numerous studies that surgical site infection (SSI) rates are significantly lower in patients who have undergone laparoscopic surgery [5].

The questions are firstly whether mechanical bowel preparation prior to surgery is effective in reducing infective complications (that includes superficial and deep surgical site infections and including anastomotic leaks) and secondly whether bowel preparation has a negative impact on fluid and electrolyte balance of patients prior to surgery that might have an adverse outcome in terms of complications and recovery. It is possible that both are correct and then we must consider the balance of risk and benefit.

There are a number of variables that need to be considered with regard to mechanical bowel preparation. The variable that is attracting the most attention and is mostly responsible for the schism in bowel preparation guidelines is the synchronous use of oral nonabsorbable antibiotics. This chapter will go on to analyze the data that exists in this area.

Arguments in Favor of Mechanical Bowel Preparation

Effective mechanical bowel preparation results in a macroscopically cleaner bowel with potentially easier bowel handling and a theoretical lower risk of gross peritoneal or wound contamination. It also results in a reduction in the quantity of bowel content at the site of anastomosis for a period of time postoperatively, or longer where the anastomosis is defunctioned with a proximal stoma.

It has been assumed that the bacterial load in the colon is reduced but this is incorrect [6]. Additionally, there is no need for a preoperative enema or distal washout of the rectum prior to inserting mechanical staplers into the rectum, and the operation itself might be seen to be aesthetically less unpleasant.

From an outcome perspective, it is believed by many surgeons that it results in a lower risk of surgical site infection and anastomotic leak. It is also believed that if patients receive bowel preparation and are defunctioned with a proximal stoma, then any leak that does occur will be easier to

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manage and have less disastrous consequences. This chapter will go on to address the evidence that exists in this area. The findings of recent meta-analyses and systematic reviews are summarized in Table 12.1 [6–15].

Lastly, while there is evidence that bowel preparation can cause significant electrolyte disturbance, there is evidence to the contrary that with modern preparations and appropriate use the risk of this can be negated [16].

Table 12.1 Summary of meta-analyses and systematic reviews regarding mechanical bowel preparation and antibiotics

Authors	Origin of study	Population/ studies included	Comparison	Outcome measures	Important findings	Limitations of study/ comments
Rollins et al. [7]	United Kingdom, *Annals of Surgery* 2018	28 RCTs, 12 cohort studies	1. Combined antibiotics + MBP vs MBP 2. Combined antibiotics + MBP vs combined antibiotics 3. Combined antibiotics + MBP vs no NMBP 4. Combined antibiotics vs NMBP 5. Combined antibiotics vs MBP	SSI, anastomotic leak, 30-day mortality, morbidity, development of ileus, *C. difficile* infection rates	Combined antibiotics with MBP showed significant reduction of all outcome measures, no increase in *C-diff* rates No difference between combined antibiotics and MBP vs combined antibiotics alone in terms of SSI and leak. Reduction in 30-day mortality and ileus Combined antibiotics with MBP associated with lowest risk of SSI	Limited data regarding comparison between combined antibiotics + MBP vs combined antibiotics alone
Toh et al. [8]	Australia, *Journal of the American Medical Association* 2018	38 RCTs	1. MBP vs NMBP 2. Combined antibiotics with MBP vs combined antibiotics 3. Combined antibiotics with MBP versus MBP	SSI, superficial and deep, anastomotic leak, mortality, readmission, urinary infections, pulmonary complications	Combined antibiotics with MBP associated with lowest risk of SSI No significant difference found in comparison between combined antibiotics with MBP versus combined antibiotics alone MBP alone conferred no benefit	Limited data regarding comparison between combined antibiotics + MBP vs combined antibiotics alone Most studies assessed open surgery
Rollins et al. [6]	United Kingdom, *World Journal of Gastroenterology*, 2018	23 RCTs, 12 observational studies	MBP vs NMBP vs rectal enema	Anastomotic leak, SSI, deep SSI, length of hospital stay, mortality	Overall analysis showed no difference Analysis of RCTs alone showed no difference Observational studies found in favor of MBP in nearly all outcome measures, although not when compared with rectal enema	Did not take into account MIS Did not take into account use of antibiotics
Dahabreh et al. [9]	United States, *Diseases of the Colon and Rectum*, 2015	18 RCTs, 7 nonrandomized trials, 6 single group cohorts	MBP vs NMBP	Length of hospital stay, quality of life and adverse events, postoperative complications	Overall analysis showed no difference	States data reporting with regard to surgical access and antibiotics poor
Güenaga et al. [10]	Brazil, *Cochrane Review*, 2011	18 RCTs	MBP vs NMBP vs rectal enema	Anastomotic leak, SSI	No statistically significant differences between MBP, NMBP, and rectal enema alone Rectal and colonic surgery analyzed separately—no significant difference	Only a small proportion of patients had minimally invasive surgery

Table 12.1 (continued)

Authors	Origin of study	Population/ studies included	Comparison	Outcome measures	Important findings	Limitations of study/ comments
McSorley et al. [11]	United Kingdom, *British Journal of Surgery*, 2018	14 RCTs, 8 observational studies	Combined antibiotics + MBP vs MBP	SSI, anastomotic leak, postoperative ileus, readmission, mortality	IOMBP significantly reduced SSI in both RCTs and observational studies Sub-analysis assessing deep space SSI, anastomotic leak rates, postoperative ileus, readmission rates, and mortality found significantly in favor of IOMBP, but only when cohort studies considered. RCTs either showed no difference or did not assess	Variations in type of MBP and antibiotic regimen used Limitations of cohort studies
Koullouros et al. [12]	United Kingdom, *International Journal of Colorectal Diseases*, 2017	23 RCTs, 8 cohort studies	1. Oral antibiotics vs intravenous antibiotics 2. Combined antibiotics + MBP vs MBP 3. Combined antibiotics vs combined antibiotics + MBP	SSI (superficial and deep)	Both RCTs and cohorts found significantly in favor of combined antibiotics versus one modality Found no difference between combined antibiotics alone vs IOMBP, both in RCTs and cohort studies	Majority of RCTs published in the 1980s Heterogeneity in antibiotics and MBP regimens
Chen et al. [13]	China, *Diseases of the Colon and Rectum*, 2016	7 RCTs	MBP vs combined antibiotics + MBP	SSI (superficial and deep)	IOMBP had statistically significant lower incisional SSI rates Equivocal result with regard to deep SSI	States studies were not blinded Reporting of antibiotic regimens poor
Allegranzi et al. [14]	World Health Organization, *Lancet*, 2016	11 RCTs comparing (1), 13 RCTs comparing (2)	1. Combined antibiotics + MBP vs MBP 2. MBP vs NMBP	SSI, anastomotic leak	IOMBP reduces SSI rate, no difference in rates of anastomotic leak Equivocal result regarding MBP vs NMBP	Heterogeneity regarding antibiotic and bowel preparation protocols
Nelson et al. [15]	United Kingdom, *Cochrane Review*, 2014	96 RCTs	1. Antibiotics vs no antibiotics 2. Oral antibiotics vs intravenous antibiotics 3. Combined antibiotics vs intravenous antibiotics 4. Timing of antibiotic doses 5. Pathogenic coverage	SSI (abdominal wound infection)	Antibiotic prophylaxis should cover anaerobic and aerobic pathogens Both OAB and IAB significantly reduce SSI, with combined regimens having the greatest effect	Did not take into account MBP

RCTs randomized controlled studies, *MBP* mechanical bowel preparation, *NMBP* no mechanical bowel preparation, *SSI* surgical site infection, *MIS* minimally invasive surgery, *IO* combined antibiotics, *OAB* oral antibiotics, *IAB* intravenous antibiotics, *IOMBP* intravenous and oral antibiotics with mechanical bowel preparation

Arguments Against the Routine Use of Mechanical Bowel Preparation

There are many mechanical bowel preparation regimes, but they all require the ingestion of large volumes of fluid. However, there are some new lower volume (1 L) bowel preparations now on the market [17].

They are undoubtedly unpleasant for the patient and can be very challenging, particularly in the elderly and frail, and are known to cause hypovolemia and electrolyte imbalance including hyponatremia, hypernatremia, hypokalemia, hypocalcemia, hypomagnesemia, and phosphate nephropathy. MBP may therefore be particularly dangerous in patients with cardiac and renal comorbidity [18, 19].

They are also variably effective, and there is a recognized failure or partial failure rate that can result in a situation that is worse for the surgeon than having no bowel preparation at all [20]. A dilated fluid-filled colon and rectum is probably more hazardous than an unprepared large bowel [21]. Furthermore, it is possible to precipitate acute bowel obstruction (albeit relatively rarely) by giving bowel preparation to patients with impending obstruction, which in itself may necessitate a change of surgical approach—usually to the detriment of the patient. There is also evidence to suggest exacerbation of postoperative ileus and impaired anastomotic healing [22].

By comparison, rectal enemas are usually well tolerated, are safe in almost all circumstances, and are generally effective in emptying the rectum and the left colon—although they may not empty the colon proximal to a stenosing lesion.

Patient Effects and Considerations

One of the principles of effective ERAS is to bring the patient to surgery in an optimized state, which includes a status of normovolemia and normal electrolyte balance. This is achieved by maintaining oral hydration and supplementation in the 24 hours prior to surgery. Mechanical bowel preparation has a capacity to disrupt this and indeed may be hazardous in patients with cardiac and renal dysfunction in particular [18, 19]. The need to purge may also cause significant sleep disturbance.

This may then impact on fluid requirement during the operative and postoperative period that may increase complications and hospital stay. Mechanical bowel preparation is often self-administered in an unsupervised environment, which may result in poor recognition of these problems and may also result in non-compliance and failed preparation. Frail patients may receive bowel preparation in hospital under supervision and be administered in conjunction with intravenous rehydration, but the overall fluid and electrolyte impact of these two interventions is difficult to gauge. Inpatient preparation also does not safeguard against significant complications [23]. Simple estimations of serum urea and electrolytes following these interventions may not accurately reflect significant disruptions in homeostasis. Patient factors that must be taken into account when considering MBP are outlined in Table 12.2.

Most colonoscopy studies report a failure rate of between 20% and 40%, with only about 1:5 patients with failed preparation reporting not following instructions adequately. This failure rate relates to inadequacy for colonoscopic purposes with reduced adenoma detection rates in particular but nevertheless gives an idea of the limitations [18, 19, 23]. Risk factors for failed or inadequate preparation are outlined in Table 12.3 [24–26]. In addition to bowel preparation not necessarily clearing the bowel adequately of stool, it is unlikely to have much impact upon bacteriology in the lumen.

Table 12.2 Patient factors when considering mechanical bowel preparation

The patient	Is the patient at high risk of dehydration and electrolyte imbalance? Is the patient immunocompromised? Is the patient at increased risk of infection? Diabetic/obese? What is the risk of failure of mechanical bowel preparation if it is administered?
The pathology	Does the patient have impending bowel obstruction? Does the patient have malignancy or inflammatory bowel disease? Is there pre-existing infection? Has the patient had preoperative radiotherapy?
The operation	Does the operation involve an anastomosis? If so, where is the anastomosis: ileocolic, colocolic, colorectal, ileo-rectal? Is the anastomosis to be defunctioned? Is the operation being performed laparoscopically or via a laparotomy?
The trials	Which bowel preparation regime is being tested? What is it being compared to—enema or none? What synchronous antibiotic regime is used? Are oral nonabsorbable antibiotics used?

Table 12.3 Risk factors for failed mechanical bowel preparation

Risk factors for inadequate bowel preparation	Instructions not followed properly Previously failed bowel preparation Procedural indication as constipation Use of tricyclic antidepressants Male patient Hospitalized patient Medical history of stroke, cirrhosis, dementia

Surgical Site Infection and Anastomotic Leak Rates

It should be noted that the question of whether any antibiotics should be used prior to colorectal surgery has been answered. The evidence is categorical that they should be administered, and controversy regarding this was laid to rest many years ago [27, 28]. There have, however, been more recent meta-analyses, the findings of which have been concordant with earlier work. In a 2014 Cochrane review, Nelson et al. found a risk ratio (RR) of 0.34 when comparing antibiotics to no antibiotics or placebo with regard to surgical wound infections (Fig. 12.1) [15].

Indeed, many recent papers that cite the use of "mechanical bowel preparation alone" in fact refer to the use of MBP with systemic antibiotics prior to surgery, but without additional oral antibiotics. Furthermore, papers that cite "no bowel preparation or antibiotics" do in fact mean that perioperative systemic antibiotics had been given, but no oral antibiotics. Therefore, for the remainder of the chapter, "MBP" refers to the administration of mechanical bowel preparation and systemic intravenous antibiotics at the time of anesthetic induction.

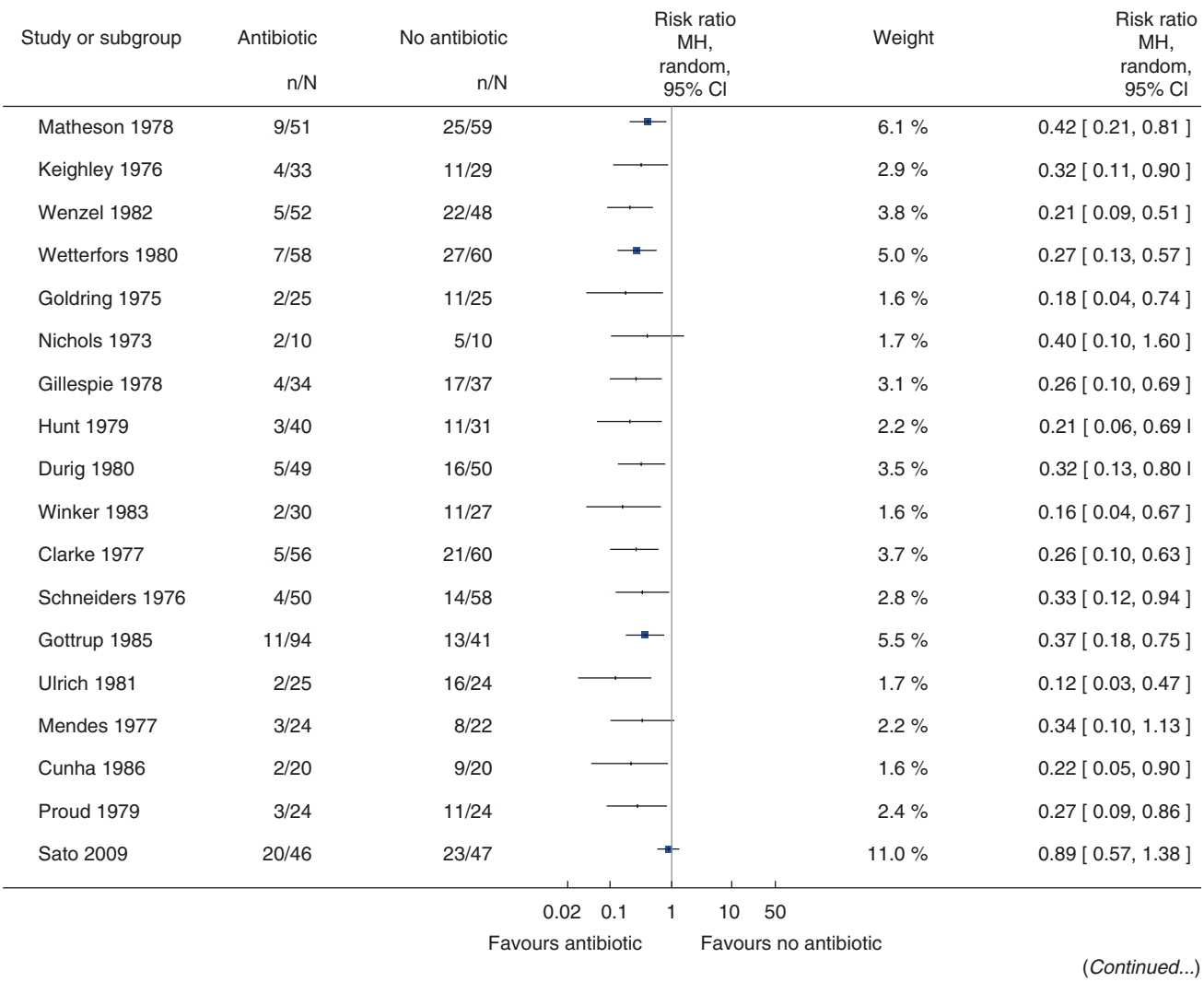
a **Analysis 1.1. Comparison I antibiotic versus no antibiotic/placebo, outcome I surgical wound infection (SWI).**

Review: Antimicrobial prophylaxis for colorectal surgery

Comparison: I antibiotic versus no antibiotic/placebo

Outcome: I surgical wound infection (SWI)

Study or subgroup	Antibiotic n/N	No antibiotic n/N	Risk ratio MH, random, 95% CI	Weight	Risk ratio MH, random, 95% CI
Matheson 1978	9/51	25/59		6.1 %	0.42 [0.21, 0.81]
Keighley 1976	4/33	11/29		2.9 %	0.32 [0.11, 0.90]
Wenzel 1982	5/52	22/48		3.8 %	0.21 [0.09, 0.51]
Wetterfors 1980	7/58	27/60		5.0 %	0.27 [0.13, 0.57]
Goldring 1975	2/25	11/25		1.6 %	0.18 [0.04, 0.74]
Nichols 1973	2/10	5/10		1.7 %	0.40 [0.10, 1.60]
Gillespie 1978	4/34	17/37		3.1 %	0.26 [0.10, 0.69]
Hunt 1979	3/40	11/31		2.2 %	0.21 [0.06, 0.69 I
Durig 1980	5/49	16/50		3.5 %	0.32 [0.13, 0.80 I
Winker 1983	2/30	11/27		1.6 %	0.16 [0.04, 0.67]
Clarke 1977	5/56	21/60		3.7 %	0.26 [0.10, 0.63]
Schneiders 1976	4/50	14/58		2.8 %	0.33 [0.12, 0.94]
Gottrup 1985	11/94	13/41		5.5 %	0.37 [0.18, 0.75]
Ulrich 1981	2/25	16/24		1.7 %	0.12 [0.03, 0.47]
Mendes 1977	3/24	8/22		2.2 %	0.34 [0.10, 1.13]
Cunha 1986	2/20	9/20		1.6 %	0.22 [0.05, 0.90]
Proud 1979	3/24	11/24		2.4 %	0.27 [0.09, 0.86]
Sato 2009	20/46	23/47		11.0 %	0.89 [0.57, 1.38]



(*Continued...*)

Fig. 12.1 (**a, b**) Antibiotic versus antibiotic/placebo, Outcome 1 surgical wound infection (SWI). (Reprinted with permission from Nelson et al. [15])

b

(*Continued...*)

Study or subgroup	Antibiotic n/N	No antibiotic n/N	Risk ratio MH, random, 95% CI	Weight	Risk ratio MH, random, 95% CI
Nygaard 1980	7/108	8/49		3.3 %	0.40 [0.15, 1.03]
Utley 1984	3/13	11/19		2.7 %	0.40 [0.14, 1.16]
Olsen 1983	5/65	16/64		3.4 %	0.31 [0.12, 0.79]
Montariol 1979	1/46	5/41		0.8 %	0.18 [0.02, 1.46]
Eykyn 1979	6/33	15/23		4.7 %	0.28 [0.13, 0.61]
Schiessel 1984	2/29	12/31		1.6 %	0.18 [0.04, 0.73]
Hagen 1980	2/17	8/21		1.6 %	0.31 [0.08, 1.27]
Höjer 1978	6/58	26/60		4.4 %	0.24 [0.11, 0.54]
Bjerkeset 1980	1/25	8/31		0.8 %	0.16 [0.02, 1.16]
Hughes 1979	12/78	31/81		7.4 %	0.40 [0.22, 0.72]
Rosenberg 1971	9/40	17/43		5.9 %	0.57 [0.29, 1.13]
Andersen 1979	1/45	5/42		0.8 %	0.19 [0.02, 1.53]
Total (95% CI)	**1278**	**1177**		**100.0 %**	**0.34 [0.28, 0.41]**

Total events: 148 (Antibiotic), 433 (No antibiotic)
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 32.94$, df = 29 ($P = 0.28$); $I^2 = 12\%$
Test for overall effect: $Z = 11.39$ ($P < 0.00001$)
Test for subgroup differences: not applicable

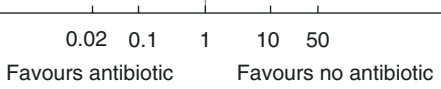


Fig. 12.1 (continued)

There are, however, three further questions regarding the outcomes of bowel preparation in relation to surgical site infection that can be addressed in the literature:

- What is the evidence that mechanical bowel preparation on its own reduces surgical site infection or anastomotic leak in colorectal resection when compared to no preparation at all or compared to rectal enemas alone?
- What is the evidence that mechanical bowel preparation when combined with the administration of oral nonabsorbable antibiotics reduces surgical site infection or anastomotic leak?
- What is the evidence that systemic and oral antibiotics without mechanical bowel preparation reduce surgical site infection or anastomotic leak when compared to mechanical bowel preparation in combination with antibiotics?

Analysis of the data is problematic for all questions because of the heterogeneity of the studies. Colonic resections with different pathologies and different anatomical anastomoses are often pooled together. Rectal anastomoses that are defunctioned are sometimes excluded. Different mechanical bowel preparation regimes are used and sometimes combined with enemas. The surgical approach (open or laparoscopic) varies and is not always quantified. There are also many retrospective database studies, analysis of which carries inherent risks of significant bias. There are, however, many recent meta-analyses that have largely assessed randomized controlled trials (RCTs). These are summarized in Table 12.1 [6–15].

Mechanical Bowel Preparation Versus No Preparation

There is extensive data available for analysis that answers the question of whether bowel preparation, with or without additional oral antibiotics, is effective or not. This includes many randomized controlled trials and observational studies.

These have all recently been subjected to a good quality meta-analysis [6]. This can be seen in the context of a previ-

ous Cochrane review [10] and meta-analyses that all have the same conclusion [9, 14, 29]. This is that there is no evidence of reduced surgical site infection rate or anastomotic leak rate with mechanical bowel preparation when compared to no bowel preparation or rectal enema alone. These conclusions are similar whether the meta-analysis includes RCTs only or if the observational studies are included. If, however, the observational studies are looked at in isolation, there is an apparent benefit that is difficult to explain.

Whether bowel preparation should be administered prior to low rectal resection with a defunctioned anastomosis is uncertain, and it remains most surgeons' practice to do so. Leaving a colon full of feces proximal to a low rectal anastomosis with a defunctioning ileostomy proximal to this seems illogical. There is some evidence that an ileostomy in itself inhibits colonic peristalsis [30]. It is therefore feasible that the combination of a rectal enema to empty the left colon and a proximal ileostomy may be as effective as full bowel prep in preventing the passage of fecal material past a newly formed rectal anastomosis, and the purported surgical complications.

There is evidence to support this theory. As discussed previously, Rollins et al. found that although RCTs showed no benefit to MBP in terms of reducing SSI, analysis of observational studies alone did show a statistically significant reduction. This, however, was negated when compared to studies that utilized a rectal enema in place of full MBP [6]. In their Cochrane review of 18 RCTs, Güenaga et al. found no difference in SSI rates or complications between MBP and rectal enema [10].

It should be noted that the overwhelming majority of patients included in these meta-analyses had at least systemic antibiotics perioperatively. A smaller proportion had additional oral antibiotics, and a smaller proportion still had oral antibiotics in isolation.

Mechanical Bowel Preparation with Combined Versus Unimodal Antibiotics

The question of whether combined antibiotics—systemic and oral—in conjunction with bowel preparation are effective at reducing SSI has also been assessed by meta-analysis in recent years. The meta-analyses have compared SSI rates with patients receiving solely systemic antibiotics and mechanical bowel preparation.

The intention of systemic antibiotics is to achieve an adequate concentration in tissues at the time of operation and opening of the colon. There is a belief, however, that intraluminal organisms are unaffected by this, therefore necessitating the use of oral antibiotics. A logical inference from this is that emptying of the colon reduces bacterial load and the three interventions combined would result in the lowest rate of SSI, and potentially other complications.

In a 2018 meta-analysis, Rollins et al. found that combined antibiotics with MBP were associated with a significant reduction in SSI risk when compared with MBP (RR: 0.51) (Fig. 12.2) [7]. This remained the case when assessing solely RCTs or cohort studies. In terms of overall analysis and when considering cohort studies, combined antibiotics were also associated with a reduced risk of anastomotic leak, 30-day mortality, and morbidity. When considering RCTs alone, there was no significant difference. Overall analysis revealed a lower risk of ileus with combined antibiotics, but not when cohort studies or RCTs were analyzed in isolation [7].

In their analysis of RCTs only, Chen et al. found that combined antibiotics with mechanical bowel prep significantly reduced SSI (7.2% vs 16%), but had no effect on organ space SSI [13]. This was in accordance with the findings of Koullouros et al., who arrived at a risk reduction (RR) of 0.48 in favor of a combined rather than unimodal regimen [12].

McSorley et al. found the same when analyzing RCTs for SSI (OR: 0.45) [11]. In addition, when analyzing observational studies, they found significantly reduced rates of anastomotic leak, postoperative ileus, readmission, and mortality. This was not replicated when RCTs were considered (Fig. 12.3) [11]. The World Health Organization (WHO) arrived at similar conclusions with regard to all SSIs, but no difference when assessing anastomotic leak rates (OR: 0.56) (Fig. 12.4) [14].

In their assessment of 19 RCTs, Toh et al. found a significant reduction in SSI rate with combined antibiotics and MBP versus MBP alone, but no difference in terms of other outcome measures (OR: 0.7) [29].

A recent Europe-wide audit by the European Society of Coloproctology (ESCP) looking primarily at anastomotic leak was found in favor of combined antibiotics in addition to MBP. Of note, it also found that less than 20% of participating centers in the study utilized this regimen [31].

This question has also been tackled by a large number of observational studies in the United States. These studies utilize data from large, regional databases concerning colorectal surgery [32–34]. They have all found in favor of combined antibiotics in addition to mechanical bowel preparation. This is the case whether their comparator is unimodal antibiotics with bowel preparation or unimodal antibiotics without bowel preparation.

As mentioned before, analysis of these studies is problematic. A large number of the cases were performed via the open approach. It is also difficult to extract data such as exact site of resection, various relevant patient factors such as comorbidity and fitness, and method of preparation used. Missing data excludes significant numbers from analysis and there is a large potential for selection and reporting bias. While not necessarily negating findings from such studies, it should qualify their interpretation.

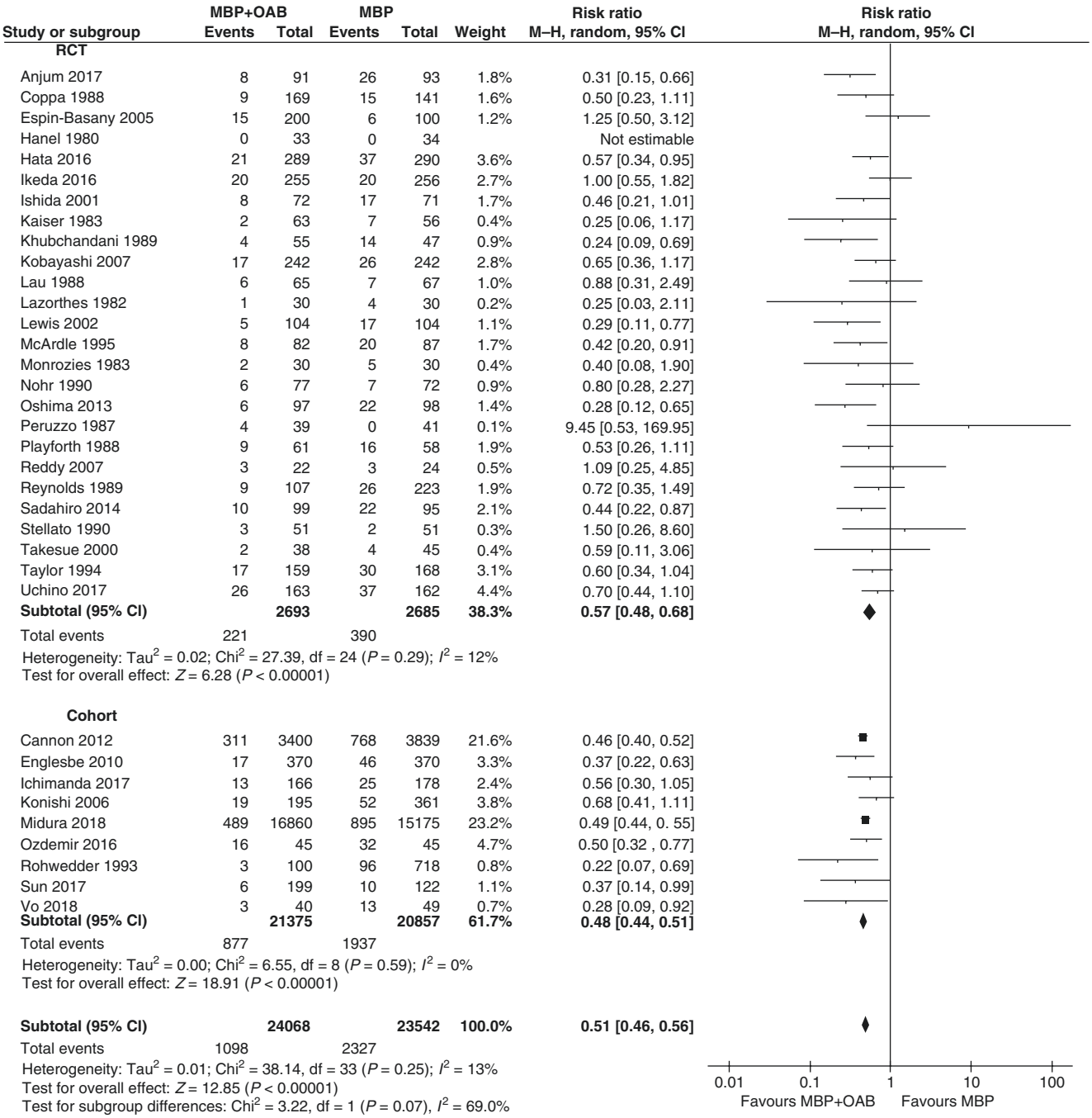


Fig. 12.2 Forest plot comparing surgical site infection rate for patients receiving MBP + OAB versus MBP alone, divided by evidence from RCTs and cohort studies. A Mantel–Haenszel random effects model was used to perform the meta-analysis, and risk ratios are quoted including 95% confidence intervals. (Reprinted with permission from Rollins et al. [7])

Systemic and Oral Antibiotics Without Mechanical Bowel Preparation

Evidence regarding this question is limited. One large retrospective database study from the United States found no benefit to MBP combined with oral and systemic antibiotics when compared with oral and systemic antibiotics alone [35]. Another study of similar methodology found that combined antibiotics in conjunction with MBP was superior [36]. Further papers addressing this issue are scarce. Although small subsets of patients fall into this group in other observational or retrospective studies, the inherent limitations remain.

In their 2018 meta-analysis—assessing four studies that looked at the issue (two RCTs and two cohort studies)—

Reference	SSI rate: Oral antibiotics	SSI rate: Control	Weight (%)	Odds ratio
RCTs				
Barber *et al.*[14]	2 of 31	3 of 28	1·7	0·57 (0·09, 3·72)
Hanel *et al.*[15]	0 of 33	0 of 34		Not estimable
Kaiser *et al.*[16]	2 of 63	7 of 56	4·2	0·23 (0·05, 1.15)
Lau *et al.*[17]	3 of 65	5 of 67	2·8	0·60 (0·14, 2·62)
Reynolds *et al.*[19]	9 of 107	26 of 223	9·1	0·70 (0·31, 1·54)
Khubchandani *et al.*[18]	5 of 55	14 of 47	8·1	0·24 (0·08, 0·72)
Stellato *et al.*[20]	3 of 51	2 of 51	1·1	1·53 (0·24, 9·57)
Ishida *et al.*[21]	8 of 72	17 of 71	9·0	0·40 (0·16, 0·99)
Lewis[22]	5 of 104	17 of 104	9·6	0·26 (0·09, 0·73)
Espin-Basany *et al.*[23]	15 of 200	6 of 100	4·4	1·27 (0·48, 3·38)
Kobayashi *et al.*[24]	6 of 242	14 of 242	8·1	0·41 (0·16, 1·10)
Oshima *et al.*[25]	6 of 97	22 of 98	12·1	0·23 (0·09, 0·59)
Sadahiro *et al.*[26]	6 of 99	17 of 95	9·6	0·30 (0·11, 0·79)
Hata *et al.*[27]	21 of 289	37 of 290	20·2	0·54 (0·31, 0·94)
Subtotal	91 of 1508	187 of 1506	100·0	0·45 (0·34, 0·59)
Heterogeneity: $\chi^2 = 13{\cdot}60$, 12 d.f., $P = 0{\cdot}33$; $I^2 = 12\%$				
Test for overall effect: $Z = 5{\cdot}88$, $P < 0{\cdot}001$				
Cohort studies				
Konishi *et al.*[28]	19 of 195	52 of 361	1·2	0·64 (0·37, 1·12)
Cannon *et al.*[29]	311 of 3400	768 of 3839	22·9	0·40 (0·35, 0·46)
Hendren *et al.*[30]	71 of 1357	281 of 2701	6·2	0·48 (0·36, 0·62)
Scarborough *et al.*[4]	48 of 1494	174 of 2322	4·6	0·41 (0·30, 0·57)
Morris *et al.*[31]	162 of 2486	452 of 3779	11·7	0·51 (0·43, 0·62)
Kiran *et al.*[33]	145 of 2324	462 of 3822	11·5	0·48 (0·40, 0·59)
Moghadamyeghaneh *et al.*[32]	31 of 1386	150 of 2248	3·9	0·32 (0·22, 0·47)
Koller *et al.*[2]	583 of 10643	1210 of 11836	37·9	0·51 (0·46, 0·56)
Subtotal	1370 of 23285	3549 of 30908	100·0	0·47 (0·44, 0·50)
Heterogeneity: $\chi^2 = 13{\cdot}45$, 7 d.f., $P = 0{\cdot}06$; $I^2 = 48\%$				
Test for overall effect: $Z = 22{\cdot}65$, $P < 0{\cdot}001$				
Test for subgroup differences: $\chi^2 = 0{\cdot}10$, 1 d.f., $P = 0{\cdot}75$; $I^2 = 0\%$				

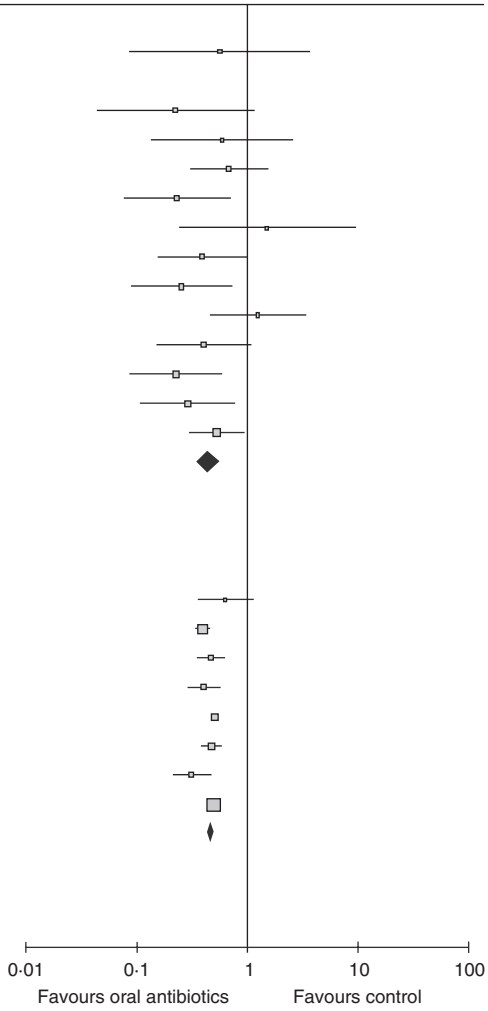


Fig. 12.3 Forest plot of studies that used preoperative oral antibiotics the day before colorectal surgery to prevent surgical-site infection (SSI). A Mantel–Haenszel fixed-effect model was used for meta-analysis. Odds ratios are shown with 95% confidence intervals. (Reprinted with permission from McSorley et al. [11])

Study or subgroup	Oral antibiotics: Events	Oral antibiotics: Total	No oral antibiotics: Events	No oral antibiotics: Total	Weight	Odds ratio M-H, random, 95% CI
Espin-Basany 2005	15	200	6	100	9.0%	1.27 [0.48, 3.38]
Horie 2007	10	46	5	45	7.3%	2.22 [0.69, 7.12]
Ishida 2001	8	72	17	71	9.6%	0.40 [0.16, 0.99]
Kobayashi 2007	17	242	26	242	12.9%	0.63 [0.33, 1.19]
Lewis 2002	5	104	17	104	8.4%	0.26 [0.09, 0.73]
Oshima 2013	6	97	22	98	9.2%	0.23 [0.09, 0.59]
Roos 2011	10	143	19	146	10.8%	0.50 [0.23, 1.12]
Sadahiro 2014	10	99	22	95	10.8%	0.37 [0.17, 0.84]
Stellato 1990	6	51	2	51	4.5%	3.27 [0.63, 17.02]
Takesue 2000	2	38	4	45	4.1%	0.57 [0.10, 3.29]
Taylor 1994	18	159	39	168	13.3%	0.42 [0.23, 0.78]
Total (95% CI)		**1251**		**1165**	**100.0%**	**0.56 [0.37, 0.83]**
Total events	107		179			
Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 20.35$, df = 10 ($P = 0.03$); $I^2 = 51\%$						
Test for overall effect: $Z = 2.85$ ($P = 0.004$)						

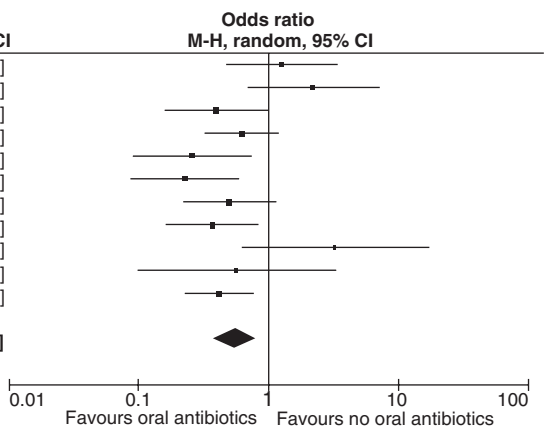


Fig. 12.4 Mechanical bowel preparation (MBP) and oral antibiotics versus MBP and no oral antibiotics, outcome surgical site infection (SSI). M-H Mantel–Haenszel (test), CI confidence interval. (Reproduced with permission from the World Health Organization [42])

Rollins et al. found no difference between combined antibiotics with MBP and combined antibiotics without MBP in terms of SSI and anastomotic leak [6]. The researchers did find a significantly lower 30-day mortality in patients who had MBP and combined antibiotics, and a lower risk of ileus. The researchers did cite concerns regarding limited data to answer this question, however [6]. Toh et al. found no significant difference between combined antibiotics with MBP versus combined antibiotics alone, but, again, the meta-analysis was subject to a limited number of studies—three RCTs [29].

As discussed by Nelson et al. in their Cochrane review, "it is not known whether oral antibiotics would still be effective when the colon is not empty" [15]. Given that evidence exists to highlight the negative aspects of bowel preparation, notwithstanding its unpleasantness, this would appear to be an area of study that should be probed with some urgency [22].

The need for this endeavor highlights another problem however. SSI rates, and indeed other commonly reported complication rates, are relatively low, and by many accounts, reducing [37]. This means that RCTs would require unfeasible numbers of patients to avoid being underpowered. The issues afflicting retrospective database analysis have previously been discussed. This therefore raises the question of how this issue could most appropriately be answered.

With regard to clinical considerations, there are legitimate concerns that routinely giving combined antibiotics to all elective colorectal patients may also increase the rate of *Clostridium difficile* infection, for example. Evidence regarding this is conflicting, and interpretation, as before, should depend on methodological quality [38–40]. There are currently few RCTs or systematic reviews directly assessing this, however, Rollins et al. found no significant difference in rates of infection when comparing patients receiving MBP and combined antibiotics versus those receiving MBP [7].

Regarding antibiotics, an exciting recent area of study concerns the idea that anastomotic dehiscence is less affected by, for example, ischemia, but rather by microbial pathogenesis. In a murine model, Shogan et al. found that topical application of antibiotics that acted on *Enterococcus faecalis*, or indeed direct deactivation of the intestinal metalloproteinase MMP 9, inhibited anastomotic leak [41]. Work in this field may have future implications for type of antibiotics used and may answer whether bowel preparation is a variable in the development of postoperative complications at all.

Site of Resection

Many of the papers discussed show that postoperative complications are more common in patients undergoing rectal surgery versus colonic resections. The use of MBP tends to be lower in colonic surgery [6, 9, 10, 34].

What is scarcely reported on, and subjected to statistical analysis, however, is whether the site of resection has a bearing on whether MBP in addition to various antibiotic regimens may be of benefit. This could be considered as something of a missed opportunity, as many of the papers report the site of resection in their demographic data.

Three review articles sub-categorized groups according to anatomical site of resection. Lobo et al. separately analyzed rectal surgery, but not colonic resections. As stated before, they found no benefit to the use of MBP [6]. Güenaga et al. separately analyzed colonic and rectal resections, finding no benefit to MBP in any site of operation [10]. Dahabreh et al. produced a similar analysis, with concordant results [9].

One of the large database studies [34] was limited to colonic surgery. As discussed before, they were found in favor of bowel preparation with concurrent antibiotic administration [33].

Though more limited in terms of numbers, the findings with regard to the utility of MBP according to anatomical site of location closely mirror those when all colorectal resections are grouped together.

Conclusion

Contemporary thinking regarding mechanical bowel preparation has altered substantially over the past 50 years. This chapter has aimed to delineate current data regarding the overall utility of MBP, in what context and with which simultaneous therapy it may be of benefit. It also highlights where gaps in the scientific literature exist.

There is substantial data that suggests MBP is potentially dangerous, particularly in the comorbid patient. This argument is compounded by the fact that there is a substantial failure rate to bowel preparation and that a poorly prepared bowel can make the operation more technically difficult for the surgeon. There are now several high-quality meta-analyses that concur that there is no benefit to MBP in isolation, both in terms of SSI and anastomotic leak.

Some papers, though few in number, have shown that any benefit to MBP versus no MBP is negated when compared to the use of a rectal enema. A rectal enema carries few, if any, of the risks of MBP and may achieve the same aim of clearing the site of anastomosis. The use of a rectal enema in the context of rectal surgery is therefore an interesting area of future study.

It seems, therefore, that mechanical bowel preparation in isolation should not be recommended. In recent years, however, the question of whether combined oral and systemic antibiotics in addition to MBP may be of benefit in reducing SSI and other complications has been raised. While not as clear-cut an answer, recent meta-analyses are starting to converge on the idea that combined antibiotics combined with MBP confer a benefit when compared with MBP in isola-

tion. This is more apparent in terms of SSI but less so with regard to other complications.

The comparison that has not been answered in the literature is whether combined antibiotics in the absence of MBP are as effective as MBP in addition to combined antibiotics. Given the potentially negative effects of MBP, and at best debatable benefit, it is an area that needs to be explored. This work should be done in the context of the theoretical potential for an increased risk of *Clostridium difficile* infection and other antibiotic-related complications.

While a falling SSI rate is certainly a cause for celebration, it makes answering the last question more difficult. Conducting a modern, adequately randomized RCT is rendered difficult owing to the prohibitively large number of participants that would be required in order to reach statistical significance. The alternative of large prospective database studies can provide useful information, but is limited in its interpretation.

Summary

The question of whether bowel preparation, with or without antibiotics, should be administered "always, sometimes, or never" cannot currently be answered definitively. However, mechanical bowel preparation on its own, in most circumstances, is almost certainly unnecessary and can be detrimental. Whether mechanical bowel preparation should be administered in order to enable or increase the efficacy of orally administered antibiotics awaits further investigation. Surgical site infection, and anastomotic leak in particular, is multifactorial, and it is possible that packages of care and surgical technique that do not include mechanical bowel preparation or oral antibiotics can produce equally good or indeed better outcomes. This is evidenced by studies from single institutions or individual series with much better outcomes than is evident in the large retrospective databases on which much of current guidance is being developed.

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Pharmacogenomics in Perioperative Care

13

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Introduction

Variation in how genes are expressed and differences in the structure and function of protein end products are the result of genetic variability between individuals. The most common type of genetic variation is the single nucleotide polymorphism, or SNP, where a common single base pair within a gene, or "wild type," is replaced by another less common base pair. The way that drugs and medications interact with this intrinsic variability is responsible for the wide range in responses to drugs given in perioperative medicine. The study of how these polymorphisms affect drug pharmacokinetics and pharmacodynamics is termed pharmacogenomics. The mechanisms by which gene polymorphisms lead to differences in drug response lie in changes to drug elimination, transport, and receptors. These differences may represent future targets for applied pharmacogenomic research. It is proposed that the application of pharmacogenomics in the clinical setting would allow clinicians to generate an individualized drug-response portrait for every patient and make medicine more efficacious and safer.

The two processes involved in drug elimination are metabolism and excretion. The most important enzyme family involved in drug metabolism is the cytochrome P450 (CYP) superfamily, which is involved in phase I metabolism. Phase I metabolism occurs mainly in the hepatocellular endoplasmic reticulum and is responsible for drug activation or inactivation via oxidation. Phase II metabolism prepares compounds for excretion via conjugation to soluble organic molecules. These compounds are then sent to the kidneys, lungs, or hepatobiliary system for excretion.

The main families responsible for human drug metabolism are CYP1, CYP2, and CYP3, with nearly 80% of drugs used today metabolized by these three families [1]. Underlying CYP protein polymorphisms and host factors—such as epigenetic factors, age, sex, and disease states—affect protein expression. This variation in polymorphisms and expression allows us to classify the enzymatic activity of individuals based on phenotype: poor metabolizers (two defective copies of the gene), intermediate metabolizers (heterozygotic alleles), extensive metabolizers (two normally functioning alleles), or ultrarapid metabolizers (more than two functional alleles). For example, an opiate prodrug such as codeine in a poor metabolizer would be unlikely to achieve analgesic effect. In a study done by Yang et al., 71% of postoperative patients with acute severe pain were CYP2D6 poor metabolizers, compared to other metabolizers [2]. Ultrarapid metabolizers, on the other hand, would convert a greater fraction of the prodrug and are at significant risk of respiratory toxicity even when given standard doses of codeine [3].

Polymorphisms in proteins involved in the transport of compounds also affect drug metabolism and phenotypic response. ABCB1, which is part of the ATP-binding cassette (ABC) family of transport proteins, is expressed on the brain capillary endothelial cells that form the blood-brain barrier. ABCB1 facilitates the transport of exogenous compounds to the brain. Polymorphisms in this transporter show variability in the respiratory-suppressive effects of opioids and have been implicated in the response to ondansetron in the setting of postoperative nausea and vomiting (PONV) [4, 5].

Drug receptor polymorphisms also represent a possible avenue for differences in pharmacodynamics between

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individuals. For example, various polymorphisms of the beta-adrenergic receptor have been identified and possible differences in response to vasoactive agents have been studied, but many of the results of these studies are largely inconclusive, with minimal clinical application thus far [6]. Pharmacogenomic research centered around the mu opioid receptor has elicited several polymorphisms that could, in effect, lead to a theoretical titrated dose specific to the SNP in question as pharmacogenomic profiles are generated for individual patients [7]. Also, polymorphisms in the catechol-o-methyltransferase (COMT) enzyme that tend to be inherited together, or haplotypes, have also been shown to indirectly upregulate opioid receptors and subsequent response to analgesics [8].

The potential for pharmacogenomics to improve medical care is substantial. Standard doses of medications do not always provide a favorable response to therapy and serious adverse events do occur at these dosages. A possible solution to preventing ineffective treatment, serious adverse events, prolonged hospital stays, permanent disability, and death may lie in the emerging field of pharmacogenomics. Discovering clinically significant polymorphisms and establishing evidence-based guidelines are essential for widespread implementation among practicing physicians (Table 13.1) [4, 5, 7, 9–25].

Table 13.1 Drugs, polymorphisms, and phenotypic effects of the genetic variant

Drug	Clinical utility	Polymorphisms	Phenotypic effect of the genetic variant
Tramadol	Management of pain severe enough to require an opioid analgesic and for which alternative non-opioid treatments are inadequate	CYP2D6	Poor metabolizers fail to exhibit analgesia and do not exhibit adverse side effects such as seizures and serotonin syndrome Ultrarapid metabolizers may experience life-threatening serotonin or opioid receptor-mediated adverse events
Codeine	Management of mild to moderately severe pain	CYP2D6	Poor metabolizers may fail to exhibit analgesia Ultrarapid metabolizers may reach high levels of morphine following low to standard dosing leading to increased risk of toxic systemic concentrations of morphine
Morphine	Management of pain severe enough for which alternative treatments are inadequate that require an opioid analgesic	ABCB1	Associations between ABCB1 polymorphisms and prolonged recovery room stays and postoperative morphine requirements [5]
		OPRM1	A118G polymorphism was associated with the requirement for postoperative opioids in Asians, but not in Caucasians [9].
Hydrocodone	Management of pain severe enough to require daily around-the-clock opioid, long-term treatment and for which alternative treatment options are inadequate	CYP2D6	CYP2D6 enzyme demethylates hydrocodone into hydromorphone, which has stronger mu receptor binding activity. Poor metabolizers may not reach desired analgesic effect with standard dosing [10]
Oxycodone	Pain management in patients for whom alternative treatment options are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain	OPRM1	Patients with polymorphisms have been reported to need more oxycodone to achieve adequate analgesia [9]
		CYP3A	Major metabolic pathway responsible for oxycodone metabolism. Strongly influenced by ethnic factors and polymorphisms affect dose escalation [11, 12]
		CYP2D6	No evidence that plasma oxycodone concentrations are affected in poor metabolizers compared to extensive metabolizers and ultra-metabolizers [13–15]
Fentanyl	Surgery: adjunct to general or regional anesthesia; preoperative medication; analgesic during anesthesia; and in the immediate postoperative period Transdermal device: acute postoperative pain Transdermal patch: management of pain in opioid-tolerant patients Transmucosal: management of breakthrough cancer pain in opioid-tolerant patients.	OPRM1	Variations in median effective dose required to exhibit analgesia among polymorphisms [7]
Propofol	Induction and maintenance of general anesthesia	UGT1A9	Higher induction dose required, higher levels of drug clearance, and longer time needed for loss of consciousness in polymorphisms [16]
		CYP2C9	Higher plasma concentration seen in polymorphisms [16]
Isoflurane	Induction and maintenance of general anesthesia	RyR1	Genetic susceptibility to malignant hyperthermia [17]

Table 13.1 (continued)

Drug	Clinical utility	Polymorphisms	Phenotypic effect of the genetic variant
Sevoflurane	Induction and maintenance of general anesthesia	RyR1	Genetic susceptibility to malignant hyperthermia [18]
Succinylcholine	Neuromuscular blockade for endotracheal intubation, surgery, or mechanical ventilation	BChE	Pseudocholinesterase deficiency is associated with increased sensitivity to the paralytic effects of succinylcholine
		RyR1	Genetic susceptibility to malignant hyperthermia [19]
		CACNA1S	Genetic susceptibility to malignant hyperthermia [20]
Ketamine	Induction and maintenance of general anesthesia and procedural sedation/analgesia	CYP2B6	Decreased enzyme binding and reduced drug clearance in polymorphisms [21]
Lidocaine	Local and regional anesthesia by infiltration, nerve block, epidural, or spinal techniques	SCN9A MCR1	Reduced efficacy in polymorphisms [22, 23]
Ondansetron	Cancer chemotherapy, postoperative, and radiotherapy-associated nausea and vomiting	CYP2D6	Decreased antiemetic effect of ondansetron when used for postoperative or chemotherapy-induced nausea and vomiting has been observed in CYP2D6 ultra-metabolizers [24]
		ABCB1	Gene polymorphisms are associated with antiemetic efficacy in the acute phase after chemotherapy [4]
Metoprolol	Angina, heart failure, hypertension, and acute myocardial infarction	CYP2D6	Poor metabolizers may have increased metoprolol blood levels, decreasing the drug's cardioselectivity [25]

Neuromuscular Blocking Agents

Both depolarizing and non-depolarizing paralytic agents have been shown to have polymorphisms that affect patient outcomes upon dosing. Succinylcholine and mivacurium, substrates of pseudocholinesterase, have polymorphic importance. Succinylcholine particularly involves the BChe (butyrylcholinesterase) gene polymorphism 209A > G; 1615G > A, which can result in prolonged neuromuscular blockade. Heterozygous expression of this variant results in a less effective plasma butyrylcholinesterase and subsequent longer (three- to eightfold) recovery time after succinylcholine administration. Prolongation was 60-fold longer in homozygous carriers. Similar findings have been reported for the variant gene and prolonged mivacurium-induced muscle paralysis [3]. Rocuronium is a non-depolarizing paralytic agent that was recently discovered to have similar clinical significance in terms of polymorphisms, specifically in the SLCO1B1 and ABCB1 genes [26]. These two genes encode transporters involved in the hepatobiliary metabolism of rocuronium, and polymorphisms in these genes result in reduced elimination and increased duration of the drug and subsequent prolonged neuromuscular blockade.

Local Anesthetic Response

Nine isoforms of voltage-gated sodium channels exist, which are targeted and blocked by local anesthetics. This action prevents the generation and propagation of action potentials in nerves and other excitable tissues, particularly of interest in the propagation of pain signals. Mutations in these sodium channels result in an altered ability for local anesthetics to work at their intended site. For example, the 395 N > K mutation in gene SCN9A results in reduced efficacy of lidocaine. An additional example occurs in cardiac tissue that is not pain related, as a loss of function mutation in the SNC5A cardiac sodium channel Na1.5 causes the Brugada syndrome. In one author's review of local anesthetic skin tests for lidocaine, bupivacaine, and mepivacaine, of almost 1200 patients interviewed, 250 had difficulty getting numb. Ninety patients were found to be numb to only mepivacaine, and 43 were numb only to lidocaine [27]. Subcutaneous local anesthetic resistance has also been attributed in part to melanocortin-1 receptor variants [28].

Inhaled Anesthetics

Malignant hyperthermia is a major concern when considering the pharmacogenomics of inhalational anesthetics. This hypermetabolic disorder of skeletal muscle has a susceptibility of 1 in 15,000 children and 1 in 50,000 adults in the general population; however, persistent evidence of familial and geographically dependent "hot spots" lead to the search and discovery of genetic influences [29]. Resulting pharmacogenomic studies have found numerous polymorphisms of the ryanodine receptor gene RYR1, with almost 50% of cases involving mutations within this gene. In addition, a mutation in the α(alpha)[1]subunit of the voltage-dependent calcium channel has been associated with 1% of North American malignant hyperthermia (MH) cases [30, 31]. At least 23 different RYR1 polymorphisms are associated with MH, with

the most severe cases having central core disease—a muscular disorder also associated with RYR1 polymorphisms [32, 33]. With this wide variety in polymorphisms coupled with the only 50% association rate, it is clinically impractical to test for MH-related polymorphisms at this time.

While MH is related to a specific functional mechanism in a calcium channel, halothane-induced hepatitis results from an immune response to metabolites produced by the cytochrome enzyme CYP2E1. This occurs in approximately 1 in 10,000 patients and, although the genetic mechanisms involved are not entirely clear, there is clear evidence that it is familial [34–36].

Physiologic responses to inhalation anesthetics vary; however, genetic mutations often only affect these responses at anesthetic concentrations much higher than those usually used in mammals. One contrasting genetic modality to note is that of gene CYP2E1 and how it relates to sevoflurane metabolism. Variations in levels of enzyme expression as a result of polymorphisms in the CYP2E1 gene can result in severe renal dysfunction [37].

An interesting clinically recognized phenomenon is the increased anesthetic requirements in redheads. Pheomelanin is the pigment responsible for producing red hair color and is produced via the MC1R gene, and this increased requirement is thought to be due to polymorphisms in this locus. Liem et al. were among the first to report a demonstrable increase in monitored anesthesia care (MAC) requirements in redheads, showing a 19% increase in desflurane partial pressure compared to dark haired individuals [38].

Response to Opioids

As discussed with previous medications, variations in metabolism, drug transport, and receptor protein binding are some of the ways in which genetics may influence the way a medication performs. This applies to opioids just the same, which will be discussed in a general and medication-specific manner. Documented variability in single nucleotide polymorphisms (SNPs) alters enzyme metabolism, transport proteins, and receptors, creating a challenging, complex problem when treating chronic pain and immediate postsurgical pain. These genetic deviations can result in altered drug metabolism and efficacy in commonly used analgesics noted in some patient populations.

Response to analgesics, specifically opioids, is not uniform in the population due to endless numbers of factors including pharmacogenomics, and thus the dosage, dosing intervals, and response to therapy are inconsistent both with physiologic response and analgesic response. These alterations in the genetic code may result in undesirable side effects, which are in some cases lethal, such as severe respiratory depression [39]. With 57 CYP genes, which are all highly polymorphic, the efficacy and toxicity of commonly used medications to treat acute and chronic pain must be closely monitored. These genetic phenotypes are classified as ultra-metabolism, poor-metabolism, intermediate-metabolism, and extensive-metabolism types based on the manner in which opioids are broken down into active and inactive metabolites [40].

Receptor-specific polymorphisms also play a role in opioid response. The opioid receptor mu 1 (OPRM1) gene encodes for the mu opioid receptor, for which several polymorphisms exist in the realm of both signal transduction and receptor binding [41]. The most data occurs for a single nucleotide substitution for adenine to guanine, which increases the affinity of beta-endorphins to the mu opioid receptor via increased binding [28, 42]. This polymorphism may protect against pain, as higher levels of binding in homozygotes have demonstrated decreased daily requirements of morphine [40, 41, 43].

Similar clinically relevant polymorphisms exist in the kappa and delta opioid receptor genes, OPRK1 and OPRD1, respectively. Variation in these loci has been linked to addiction and dependence to heroin, cocaine, alcohol, and opioids [44, 45]. Addiction research may use these polymorphisms to prevent opioid reinforcement and these may be future targets for patient-dependent targeted addiction therapy [27].

CYP2D6 is a highly relevant cytochrome gene, as drugs reliant upon CYP2D6 for analgesic effect include codeine, tramadol, hydrocodone, and oxycodone. According to Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines, if an individual is a known poor or ultra-metabolizer, alternative analgesics that are not dependent upon CYP2D6 metabolism should be considered, including morphine or non-opioid analgesics [46].

Codeine

Codeine is a prodrug that undergoes metabolism by CYP2D6 into morphine, which accounts for about 10% of the overall elimination pathway. As previously discussed, CYP2D6 is a highly relevant cytochrome enzyme secondary to numerous discovered polymorphisms, resulting in highly variable CYP2D6 enzymatic activity among individuals. Both poor (PM) and ultra-metabolizers (UM) for codeine exist, resulting in either increased or decreased amounts of its breakdown product morphine in the blood. In addition, response to codeine can be influenced by CYP2D6 variants as well as opioid receptor variants. Due to the significant toxicity concerns that result from these polymorphisms, CPIC guidelines strongly recommend that CYP2D6 UMs and PMs should avoid codeine due to the increased risk of toxicities and lack of analgesic effects, respectively. Additionally, the US Food and Drug Administration (FDA) warns against the use of

codeine in obese adolescents or those with obstructive sleep apnea or severe lung disease due to respiratory depression concerns [47]. In 2013, the FDA announced a black box warning against the use of codeine to manage postoperative pain in children following tonsillectomy with or without adenoidectomy [48]. This was in response to codeine-related deaths [49, 50] and serious adverse drug reactions [51] in children who were ultrarapid metabolizers.

Morphine itself is a well-established, strong opioid that binds to the mu receptor and is commonly used to treat acute and chronic pain states. It is metabolized via glucuronidation, specifically the hepatic isoenzyme UGT2B7. Several polymorphisms have been identified that potentially affect morphine's ability to adequately treat pain and may be responsible for adverse reactions such as respiratory depression. The P-glycoprotein transporter encoded by ABCB1 transports morphine across the blood-brain barrier, and polymorphisms detected in this gene result in variable ability for morphine to create respiratory depression [5].

Fentanyl

In contrast to codeine, fentanyl is metabolized by the polymorphic CYP3A4 and CYP3A5 enzymes. The polymorphisms in the *CYP3A5* (*CYP3A5*3*) gene as well as the *ABCB1* (1236C > T, 2677G > A/T, and 3435C > T) genes on fentanyl metabolism lead to significant changes in plasma concentration of fentanyl. Fentanyl levels were approximately twice as high in *CYP3A5*3* homozygotes compared to *CYP3A5*1* carriers. Response to fentanyl, like codeine, can be altered by opioid receptor and *COMT* polymorphisms. *OPRM1*(118A > G) and *COMT* (Val158Met, G > A) polymorphisms can result in increased or decreased response to fentanyl depending on genetic profile, although several studies have been conducted without success in piecing apart the true pharmacogenetic profile [52–55]. Despite these documented polymorphisms, no statistically significant findings have been reported for fentanyl-related adverse effects and genetic polymorphisms [56].

Hydrocodone

Hydrocodone, like codeine, undergoes extensive metabolism by CYP2D6 but is also metabolized by CYP3A4 to norhydrocodone, which is further conjugated by UGTs into water-soluble metabolites that are primarily excreted by the kidneys. CYP2D6 metabolizes hydrocodone to hydromorphone.

In one study, patients with the CYP2D6 UM phenotype had approximately a tenfold increase in the plasma concentration of hydromorphone compared to individuals with the CYP2D6 PM phenotype [47]. This can significantly alter how these patients experience pain response and analgesic effects. The influence of polymorphisms in *OPRM1* on pain response was also assessed in a study where patients with the AA genotype for *OPRM1* had significant association with pain scores, hydrocodone total daily dose, and hydromorphone plasma concentration [57]. Hydromorphone tightly binds to the mu receptor and demonstrates variability in serum concentrations, which correlate to polymorphisms in the OPRM1 genotype [40]. Patients homozygous for the AA allele of the OPRM1 gene demonstrate an association with pain relief and total hydrocodone dose; whereas, patients with the AG or GG alleles did not show the same association [57]. As previously mentioned, polymorphisms in *CYP2D6* had a significant impact on the analgesic effects of hydrocodone as demonstrated in another study, resulting in the FDA releasing a warning considering this phenomenon [58]. A case of respiratory depression with hydrocodone that resulted in the death of a 5-year-old child contributed to the release of this document. The child had *CYP2D6* genotype (∗2/∗41) and concomitant treatment with clarithromycin—a potent inhibitor of the CYP3A4 pathway involved in hydrocodone metabolism [59].

Methadone

Methadone is metabolized by cytochrome CYP2B6, which like other cytochrome enzymes has highly polymorphic gene encoding for it, with more than 38 variants identified thus far, which primarily arise from SNPs [60]. The *CYP2B6*6* (516 G > T, 785 A > G) is by far the most studied variant and is a significant genetic determinant of the variability in methadone elimination [61, 62]. Moreover a pharmacokinetic study showed *S*-enantiomer clearance (ml/kg/min) was significantly lower in patients with the *CYP2B6*1/*6* and *CYP2B6*6/*6* genotypes compared to those who had the *CYP2B6*1/*1* genotype without variation in *R*-enantiomer clearance [61].

Tramadol

CYP2D6 also affects tramadol, a weak opioid analgesic that is metabolized to O-desmethyltramadol and (+) and (−) tramadol. O-desmethyltramadol binds the mu opioid receptor, whereas (+) and (−) tramadol inhibits the reuptake of serotonin and noradrenaline resulting in a wide range of clinical effects [40]. CYP2D6 poor metabolizers have been shown to be protected from adverse side effects such as seizures and serotonin syndrome, but fail to exhibit analgesia in response to tramadol due to their metabolic profile. In contrast, ultrametabolizers may have life-threatening adverse reactions and

higher peak plasma concentrations of O-desmethyltramadol and exhibit greater analgesia and higher incidence of nausea [40, 63].

Oxycodone and Oxymorphone

Oxycodone is metabolized by CYP3A4 and CYP2D6 into noroxycodone and oxymorphone, respectively. CYP2D6 poor metabolizers, like other opioids, have a lower peak concentration of oxymorphone following a dose of oxycodone compared to extensive metabolizers and thus results in lower analgesic response and lower rates of opioid-related side effects [15, 64]. These patients report a 20-fold reduction of effects compared with extensive metabolizers [42]. On the other end of the spectrum, UMs reported up to a sixfold increase in analgesic effects of oxycodone compared to extensive metabolizers and concurrently have increased toxicity and adverse events. Evidence also suggests that CYP3A inhibition significantly increases oxycodone toxicity and analgesic efficacy [40].

Buprenorphine

CYP3A4 governs the metabolism of buprenorphine, a semisynthetic opioid with a connection between its role at the OPRD1 receptor and favorable treatment outcomes with heroin addiction. Specific SNPs rs58111 and rs529520 have been predictive of outcomes for opioid dependence with buprenorphine management [65]. The GG genotype at rs58111 in female opioid addicts had more favorable responses when treated with buprenorphine compared with the AA genotype and the AG genotype [40]. This unique modality and use of buprenorphine can be quite beneficial in developing targeted addiction therapy.

Malignant Hyperthermia

Malignant hyperthermia (MH) occurs as frequently as 1 in every 10,000 anesthetics, though genetic abnormalities that contribute to the development of MH may be as prevalent as 1 in 2750 individuals [66]. Many genes may be implicated in developing MH, but only the RYR1 and CACNA1S genes have been definitively associated with predisposition to MH. The RYR1 gene encodes the ryanodine receptor. Of the more than 400 variants identified of RYR1, at least 34 are known to increase susceptibility to MH [19]. The CACNA1S gene encodes the α(alpha)1 subunit of the dihydropyridine receptor (DHPR), and there are only two variants in CACNA1S associated with MH [66]. MH susceptibility is associated with several myopathies due to RYR1 defects. The co-occurrence of the two is estimated to be about 30% of patients with RYR1 myopathies [67]. Diseases predisposing patients to MH susceptibility include central core disease, multi-minicore myopathy, congenital myopathy with cores and rods, and centronuclear myopathy, among others.

Benzodiazepine Response

CYP3A4/5 and CYP2C19 are the major metabolizers of benzodiazepines, which are used to reduce anxiety and induce drowsiness preoperatively [68]. Diazepam is metabolized to its active metabolite temazepam by CYP3A4 and to desmethyldiazepam via CYP3A4 and CYP2C19. Desmethyldiazepam and temazepam are both converted to oxazepam by CYP3A4 and CYP3A4/CYP2C19, respectively. Patients with the m1 variant of CYP2C19 have lower clearance of diazepam, causing increased plasma levels and half-life [68]. CYP3A4 and CYP3A5 are the primary metabolizers of midazolam. The CYP3A5∗3 homozygous genotype yields a 50% greater enzyme induction [28].

Nausea and Vomiting

Several genetic polymorphisms that are associated with an increase in postoperative nausea and vomiting (PONV) have been identified. Polymorphisms implicated in PONV include the Taq1A polymorphism of the dopamine D2 receptor gene, a deletion in both alleles of the 5-HT3B receptor gene, alterations in the ABCB1 gene, and three or more functional alleles of CYP2D6 [69, 70]. 5-Hydroxytryptamine (5HT3) antagonists, such as ondansetron, are metabolized by CYP2D6 and may be given to patients following general anesthesia to reduce PONV. Ultrarapid CYP2D6 metabolizers (UM) have increased turnover of 5HT3 antagonists, causing increased PONV relative to poor metabolizers (PM), intermediate metabolizers (IM), and extensive metabolizers (EM). Candiotti et al. studied 250 female patients given prophylactic ondansetron following general anesthesia, and the incidence of postoperative vomiting was reported to be 45.5% in UM subjects—significantly greater than that of PM, IM, and EM patients (8.3%, 16.7%, and 14.7%, respectively) [71]. Another study of 112 patients receiving ondansetron after general anesthesia observed that patients identified as PMs exhibited less PONV despite receiving higher doses of opioids when adjusted by weight [72]. The AAG deletion in the -HT3B receptor gene also reduces the efficacy of ondansetron [73].

Cardiovascular/Coagulation Pharmacogenomics

CYP2D6 is involved in the metabolism of several β(beta)-blockers for elimination. Most notably, CYP2D6 contributes to 70–80% of metoprolol metabolism, converting metoprolol to its inactive metabolites [74]. Conversely, CYP2D6 converts carvedilol to its active metabolites. There are nearly 80 polymorphic variants of CYP2D6, some of which are known to cause a loss of function of the enzyme. Variants in CYP2D6 resulting in decreased function include CYP2D6∗10 (present in 40% of Asian descendants) and CYP2D6∗4 (present in 20% of European descendants) [75]. A 2017 study by Luzum et al. reported a lower tolerated maintenance dose of metoprolol and a higher tolerated maintenance dose of carvedilol in CYP2D6∗4 variants relative to those without the allele, which corresponds to the role of CYP2D6 in their metabolism [75]. Although some studies demonstrate variants of CYP2D6 resulting in altered efficacy of β(beta)-blockers, the evidence surrounding the clinical significance lacks consistency. Some studies reported no difference in frequency of adverse events between CYP2D6 variants during treatment with metoprolol [76, 77], while others reported significant differences in the clinical effects of variations in CYP2D6 alleles [74, 75, 78–81].

Warfarin is the most prescribed anticoagulant worldwide [82]. Its target is the vitamin K epoxide reductase complex, which is encoded by the gene VKORC1. Warfarin is a racemic mixture, and S-warfarin is 3–5 times more potent that R-warfarin. Warfarin limits the availability of reduced vitamin K, thus resulting in less circulating active clotting factors. Challenges in dosing warfarin are due to its narrow therapeutic window and wide variability in dose requirements for each individual [82]. Genes that warrant tailoring of warfarin doses include CYP2C9 and VKORCI. CYP2C9 is the primary metabolizer of S-warfarin. Both the CYP2C9∗2 and CYP2C9∗3 alleles yield reduced CYP2C9 metabolism, with the CYP2C9∗3 allele resulting in the greatest reduction of warfarin metabolism [83, 84]. Impaired metabolism results in an increased half-life of warfarin and a reduced dose of warfarin required by individuals with defective alleles. Variations in the target enzyme of warfarin, vitamin K epoxide reductase complex, are also significantly associated with warfarin sensitivity. For example, carriers of at least one copy of the VORC1 1173C > T polymorphism were found to have a significantly increased bleeding risk following anticoagulation therapy [85]. Furthermore, substitution of A for G at position -1639 results in increased warfarin sensitivity. Homozygotes for this allele have markedly increased sensitivity compared to -1639AG heterozygotes, and both AA and AG genotypes are more sensitive than the wild-type GG genotype. The homozygous -1639AA genotype is more prevalent in Asian populations than Caucasian populations [86].

Clopidogrel is an inactive prodrug that requires conversion via CYP2C19 to its active metabolite. It functions as an antiplatelet agent that irreversibly inhibits platelet activation. CYP2C19 poor metabolizers are individuals who carry two nonfunctional copies of CYP2C19. CYP2C19 poor metabolizers are of higher prevalence in Chinese populations, with approximately 14% of Chinese individuals being poor metabolizers, compared to 2% of Caucasians and 4% of African Americans [87]. In 2010, the FDA issued a black box warning regarding the inefficacy of clopidogrel in CYP2C19 poor metabolizers and advising to consider alternate antiplatelet therapy for these individuals. Meta-analyses have come to contradicting conclusions regarding the effect of CYP2C19 polymorphisms on cardiovascular events. One meta-analysis in 2009 concluded that individuals carrying CYP2C19 loss-of-functioning alleles had higher rates of cardiovascular events after treatment of clopidogrel following acute myocardial infarctions [88]. This study was supported by results of another meta-analysis in 2010, which concluded that possessing even one dysfunctional copy of CYP2C19 is associated with adverse cardiovascular outcomes [89]. Two additional studies in 2011 reported the opposite. Holmes et al. concluded that there was no association with the CYP2C19 genotype and cardiovascular events [90], while Bauer et al. reported the lack of evidence supporting CYP2C19 genotype-guided antiplatelet treatment [91].

Summary and Future Directions of Pharmacogenomics

The "one size fits all" dosing of medical therapy is inherently limited in its utility as a patient's response to a drug is unknown until after the fact. Preventing ineffective treatment, serious adverse events, prolonged hospital stays, permanent disability, and death are goals that may be achieved through the study and implementation of pharmacogenomics. This also may lead to the development of new drugs, insights into disease, and identification of predisposed individuals—all leading to more effective treatment and disease prevention. There are multiple challenges ahead, however. With the exception of CYP2D6 polymorphisms and their metabolism of analgesics, there is a lack of well-conducted clinical studies designed to provide evidence-based practice guidelines for screening optimal dosing and risk of adverse events. Other medical disciplines have been able to assess recommendations based on pharmacogenomic data. Kaufman et al. was able to use a modified AGREE (Appraisal of Guidelines for Research and Evaluation) II instrument to develop an assessment for the most commonly prescribed

cardiovascular drugs in the United States [92]. Further studies incorporating assessment of pharmacogenomic data and correlations with perioperative outcomes are necessary. The Clinical Pharmacogenetics Implementation Consortium seeks to provide peer-reviewed, updated, evidence-based, freely accessible guidelines for gene/drug pairs and proposes the following framework for evaluation of evidence supporting the impact on clinical practice: "...a sound scientific rationale linking genomic variability with drug effects, the therapeutic index of the involved medications, the severity of the underlying disease, the availability of alternative dosages or drugs for patients with high-risk genotypes, the availability of CLIA-approved laboratory tests, and peer-reviewed clinical practice guidelines that incorporate pharmacogenetics in their recommendations."[93] CPIC has also instituted a grading scheme to evaluate quality of evidence that is consistent with the National Academy of Clinical Biochemistry and the strength of recommendations according to the National Institutes of Health.

In addition, the successful implementation of pharmacogenomics rests in the availability and practicality of genetic testing. Currently, commercially available point-of-care genetic assays employ the use of microarrays and real-time polymerase chain reaction (PCR). These take hours to days to complete and could possibly lead to delays in treatment [94]. If incorporated into the standard of care, point-of-care testing needs to provide results on the order of minutes. Additionally, pharmacogenomic data can be gathered in the preoperative assessment, or as part of a patient's surgical clearance.

Another hurdle is the sheer amount of capacity required to handle pharmacogenomic data. Inclusion of raw whole-sequence genetic data of patients into the electronic medical record (EMR) is not feasible. The estimated storage requirement for genomic data is as much as 2–40 exabytes in 2025 (2–40 billion gigabytes) [95]. Including only clinically pertinent biomarkers with strong evidence of potential for a modification in the perioperative regimen is necessary to decrease the data storage and data handling burden. Physician collaboration with EMR software vendors will be necessary to develop algorithms and templates that provide pharmacogenomic testing results and clinical decision tools that highlight key results and recommendations. Accessible databases that are confidential and easy to navigate are also necessary to store this information as pharmacogenomic screening is implemented into clinical practice. Pharmacogenomic data collected by a pediatrician or family medicine physician should be available to the anesthesiologist to use in the perioperative setting at the point of care.

In the forefront of today's medical system are the issues of cost and value. Currently, in Europe and the United States, reimbursement of pharmacogenomic testing and guided clinical treatment is limited. This is most likely related to a lack of strong evidence of benefit in mortality and morbidity end points [96, 97]. Patients often pay out of pocket for these tests. Pharmacogenomic-guided treatment that shows improvement in patient outcomes, together with the decreasing costs of screening, may lead to reimbursement of pharmacogenomic-based interventions. Furthermore, healthcare institutions will be more likely to support infrastructure required to implement pharmacogenomic-guided perioperative care as cost savings and value are realized.

As discussed in this chapter, the proper sedation, intraoperative management, and postoperative medical therapy of surgical and critical care patients are paramount in the setting of enhanced recovery pathways. Tailoring medical therapy to an individual's genome is possible with the potential to develop new drugs based on the contribution of drug-response phenotype discovery. New insights in disease progression and identification of predisposed individuals may also offer better ways of illness prevention.

Conclusion

Tailoring medication choices and dose regimens to a patient's pharmacogenomic profile may be a large part of the future of anesthesiology. Individualized care based on polymorphisms in the genetic code will ultimately decrease the incidence of adverse events and hospital length of stay, increasing patient satisfaction and saving healthcare dollars. While pharmacogenomics and its application to anesthesiology are still in its infancy, different polymorphisms and their significance to clinical practice are discovered daily. Realization of this opportunity to advance anesthesia practice is vital.

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Part III

Intraoperative Management

14 Anesthetic Management and the Role of the Anesthesiologist in Reducing Surgical Stress and Improving Recovery

William J. Fawcett

Introduction and Rationale

Full recovery following major surgery is complete when the inevitable postoperative functional decline has returned to the preoperative baseline values. The duration and magnitude of this functional decline broadly mirror the magnitude of the perioperative stress response. While this sounds like a relatively straightforward concept, the precise measurement of these two variables—functional decline and the perioperative stress response—is complex.

In order to get a perspective on the progress that has been made over the last quarter of a century, it is worthwhile considering the changes that occurred in a patient undergoing major abdominal surgery prior to the advent of enhanced recovery after surgery (ERAS). Following a prolonged fast (sometimes 12 or more hours) and mechanical bowel preparation, the patient arrived for surgery in a state of dehydration, ketosis, and psychologically distressed. Then, anesthesia and surgery took place, which included a large incision, much handling of the bowel, blood loss, and intravenous (IV) fluids that were often guided by several methods such as an algorithm (e.g., *x* ml/kg/hr), central venous pressure monitoring, urine output, heart rate, or blood pressure. Analgesia was provided by an epidural or by copious systemic opioids. The insertion of nasogastric tubes, drains, and a urinary catheter was a routine. Postoperatively, large amounts of intravenous fluids were administered until bowel function returned. Prolonged analgesic requirements with delayed mobilization necessitated a hospital stay typically of 10–14 days duration. The return to functional normality—such as normal activity and return to work—could therefore be several weeks or even months. The above processes were governed by decades of unchallenged dogma.

So what changed? Practically every aspect of care. At the very heart of this was challenging every step of the aforementioned pathway, continually asking "what is the evidence for this?" and "can it be done any better?"

For many people the introduction of minimal access surgery (MIS) is seen as the only real change for the development of ERAS. While no one would disagree that laparoscopic and robotic surgery has had an enormous impact on the success of ERAS, it is worth remembering that the early descriptions of ERAS predated MIS for both cardiac and colorectal surgery [1, 2]. Moreover, even if MIS is not possible, adherence to an ERAS pathway for open surgery still confers significant and demonstrable physiological benefits to patients in terms of length of stay (LOS) [3] but also the preservation of postoperative immune function and aspects of the surgical stress response [4]. Thus, at the very heart of ERAS are the understanding, measurement, and minimization of the surgical stress response that accompanies major surgery.

The Surgical Stress Response

The classical stress response is a complex array of changes that take place following both major surgery and other pathophysiological insults such as burns, major trauma, and sepsis [5]. For many, the grandfather of our understanding of the stress response originates from Glasgow, Scotland, by Sir David Cuthbertson. In a series of studies conducted nearly 90 years ago on patients who underwent bed rest while receiving a fixed diet, he described how stool and urine analysis during bed rest reveals a slight loss of many substances, including calcium, phosphorus, nitrogen, potassium, sulfur, and creatine. However, when the same protocol was applied to patients with long bone fractures, he discovered a larger increase in the aforementioned substances in particular nitrogen (as urea), although calcium excretion did not increase much more. With the recognition that these intracellular losses were in excess of those accountable by the primary injury alone, he concluded that there was a generalized reaction occurring within the body, which caused breakdown of lean tissue (particularly muscle) and simultaneous fever [6].

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Later he described and correlated these catabolic changes with increased oxygen consumption, and the concept of ebb and flow was established relating to a decrease and increase in metabolic activity, respectively, and has more recently been described [7].

With advances in our understanding and measurement of the physiological changes that occur perioperatively, many of these stress response changes have been clearly identified and described (Table 14.1, Fig. 14.1). Broadly, the classical stress response may be divided into two major components. Firstly, there is a systemic neuroendocrine response with the concomitant metabolic sequelae. This part of the response is characterized by sympathetic nervous system and pituitary activation resulting in a large number of predictable metabolic consequences including catabolism, insulin resistance (IR), and hyperglycemia. The second major component is the inflammatory and immunological changes, initiated from

Table 14.1 The classical "stress response" to major surgery

Changes	Examples
1(a) Neuroendocrine	Pituitary and adrenal activation, e.g., ACTH, GH, cortisol, adrenaline
1(b) Metabolic consequences of 1(a)	Catabolism and nitrogen loss Insulin resistance and hyperglycemia Lipolysis Sodium and water retention Potassium loss
2) Inflammatory (both pro-inflammatory and anti-inflammatory)	SIRS response Cytokines production, e.g.: Interleukins (especially IL-6, also IL-1, IL-8) TNF alpha CRP Interferons VEGF

ACTH adrenocorticotrophic hormone, *GH* growth hormone, *SIRS* systemic inflammatory response syndrome, *IL* interleukin, *TNF* tumor necrosis factor, *CRP* C-reactive protein, *VEGF* vascular endothelial growth factor

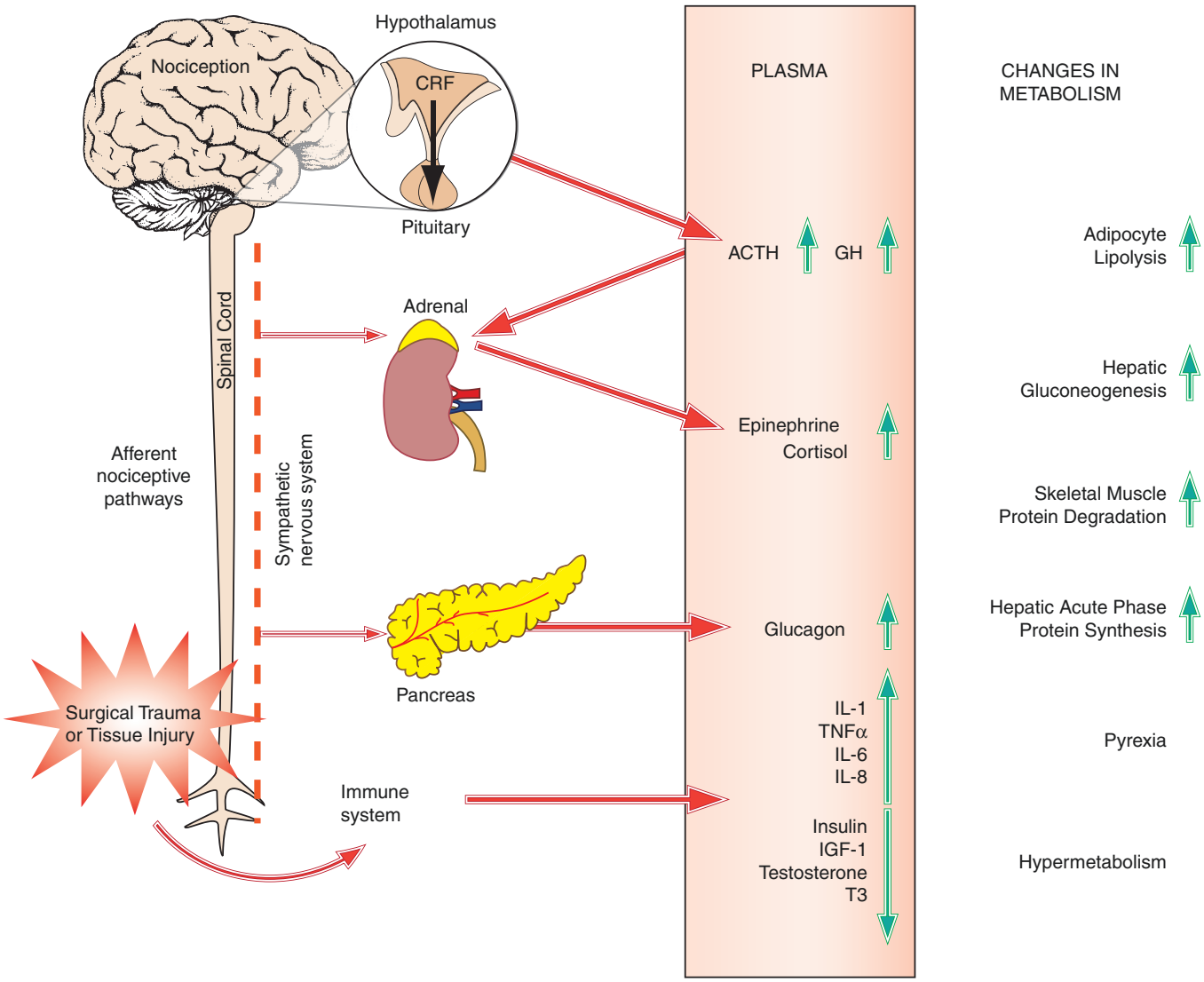

Fig. 14.1 Surgical stress responses. CRF corticotrophin-releasing factor, ACTH adrenocorticotrophic hormone, GH growth hormone, IL interleukin, TNFα tumor necrosis factor alpha, IGF insulin-like growth factor, T3 *triiodothyronine. (Adapted with permission from Dr. R. Durai, Slide 14,* https://www.slideshare.net/surgerymgmcri/metabolic-response-to-injury-14-0316)

macrophages, fibroblasts, and endothelial cells, which results in cytokine release such as interleukins (IL), tumor necrosis factor (TNF), and interferons (IFNs), which have both local and systemic effects, including malaise and fatigue. There are both pro-inflammatory and anti-inflammatory pathways initiated, with the former more attributed to complications and organ dysfunction and the latter involved in postoperative infections [8].

While this distinction between neuroendocrine/metabolic and inflammatory is convenient, it does represent an oversimplification, as there is overlap/interplay between these two components. In addition, while the magnitude of the measured stress response (vide infra) is broadly proportional to the magnitude of surgery, there is an array of other events that may magnify this response still further and include starvation, infection, hypovolemia, hypothermia, postoperative complications such as infections, postoperative nausea and vomiting, and sleep disturbances [9].

The stress response has been extensively investigated. While its effects are readily understood as an evolutionary adaptive process (e.g., such as substrate mobilization and conservation of water for an injured animal unable to have free access to nutrition and water), there is no doubt that viewed within the context of modern perioperative care, it confers very little, if any, benefit and with the potential for serious harm (Table 14.2). Moreover, as anesthesiologists, we are now focusing on long-term outcomes following oncological surgery.

The time course of these changes is variable: it may vary over a few hours (e.g., IL-1) to several days, but in uncomplicated major surgery, by 72 hours, much of the physiological upset has returned to normal. Thus, stress response reduction is seen as a key physiological change to both improve recovery and reduce short- and long-term complications.

Table 14.2 Clinical consequences of unmodified stress responses

Pathophysiology	Clinical sequelae
Catecholamine excess	Tachycardia, hypertension, cardiac ischemia
Nitrogen loss	Muscle breakdown Weakness, poor mobilization
Insulin resistance from pituitary and adrenal activation, reduced insulin secretion	Hyperglycemia ("diabetes of injury") with its risks: infections, (surgical site, respiratory, urinary) neuropathy, AKI, reoperation
Marked inflammatory changes	Infection Organ dysfunction Cognitive changes Sleep dysfunction Immunosuppression with potential for: Possibly reduced long-term cancer survival Possibly a reduction postoperative infections

AKI acute kidney injury

Assessment of magnitude of the stress response from the myriad of physiological changes described above is clearly complex. Measurements of neuroendocrine and metabolic response metabolic sequelae include either the hormones themselves—plasma concentration of cortisol, growth hormone, catecholamines, insulin, etc.—or the other metabolic changes, such as hyperglycemia, nitrogen loss, and, in particular, IR. Measurement of the inflammatory response includes C-reactive protein (CRP), interleukins, and TNF.

Stress Response Modification: Theory

Given the potential for harm arising from the aforementioned changes, it is logical that various ways have been described in which the stress response can be reduced, ameliorating physiological disturbance and promoting early recovery and reduced complications.

Minimal Invasive Surgery

The magnitude of the stress response is determined by both the magnitude of surgery and the surgical approach (open or MIS), with both the endocrine/metabolic response and in particular the inflammatory response being substantially reduced by lesser surgeries and also by MIS [10]. This is seen as a major advantage for MIS, but as the choice of the surgical route is not controlled by the anesthesiologist and will not therefore be considered further here, nor will the decision whether or not still use drains, tubes, mechanical bowel preparation, etc., all of which may add to stress response, but are usually under the direction of the surgical team [9] (see Chap. 19).

Opioids

Studies from 60 years ago demonstrated that opioids may modify both diurnal hormonal and metabolic changes in subjects [11], with later studies showing that very-high-dose opioids (e.g., 50–100 mcg/kg) may substantially reduce hormonal and metabolic responses to surgery, especially pelvic and upper abdominal surgery [12]. However, such large doses of opioids have no place within modern ERAS programs, with their principal use where postoperative lung ventilation is to be used and so is restricted for specific major procedures, e.g., cardiac surgery. Moreover, a major theme within ERAS programs is the use of multimodal or balanced, opioid-sparing analgesia [13], so while high-dose opioids are of great theoretical interest, they are of little practical interest. The introduction of shorter-acting opioids such as remifentanil predictably also lowers the intraoperative adrenal

and sympathetic activation in a dose-dependent manner [14], but the effects will be transient given the very short half-life of remifentanil.

Neuraxial Blockade

Given the neural pathway involved in neuroendocrine activation, it is logical that it can be dramatically obtunded by comprehensively blocking that pathway to prevent the subsequent pituitary and adrenal activation. The most well-described approach is neuraxial block (spinal and epidural anesthesia) with local anesthetic. Thoracic epidural anesthesia (TEA) holds a unique place within the history of ERAS, as it was this technique that was popularized by Kehlet and his colleagues more than 20 years ago with some of the first papers in this area, with patients undergoing major large bowel resection experiencing improved pain control, improved mobilization, and shortened ileus [2, 15].

A wealth of data was produced on the impact of neuraxial anesthesia on the hormonal and metabolic response to major surgery demonstrating that:

- The blockade has to be instituted prior to the start of surgery and continued well into postoperative period (i.e., several days) to obtund the responses [12].
- Blockade has to be with local anesthesia—neuraxial block with opioids has only minor effects on this process (glucose and cortisol) [16].
- If the block becomes ineffective or short-lived—such as a spinal anesthetic—the modifying metabolic effects will be transient, and the patients will thereafter have a similar response to those in whom there was no block [17].
- If the block is started following the surgical stimulus, there is some subsequent response modification [16] even in patients having TEA started following cardiopulmonary bypass (CPB), which is a major inducer of the stress response [18].
- TEA is very effective at obtunding responses for both pelvic and lower abdominal surgery but has less of a modifying effect for surgery involving the upper abdomen, presumably due to insufficient afferent blockade [16].
- TEA has no consistent effect on the inflammatory response as this is principally determined by mechanisms from the site of surgery itself, although the complex interplay between the two mechanisms may account for some the described blunting of the inflammatory response with epidurals [19].

However, in the last 10 years or more, there has been an abrupt decline in the use of epidurals for major elective surgery due to a number of factors. Firstly, other techniques of neural block have been used that provide good analgesia but without the side effects of epidurals (vide infra). Secondly, the advent of small incision surgery and MIS has rendered the use of relatively prolonged (and invasive) TEA not necessary. Finally, while epidurals have been shown to have a number of benefits (Table 14.3), their disadvantages are increasingly recognized [20].

Table 14.3 Advantages of epidurals

Benefits of epidurals
Reduced hormonal and metabolic response to surgery
Superlative, segmental analgesia
Reduction in postoperative thromboembolism
Reduced blood loss

Table 14.4 Disadvantages with epidurals

Concerns within ERAS
Failure rate
Fluid management/hypotension
Reduced mobility (especially lumbar epidurals)
Permanent neurological injury (rare) from coagulopathy/sepsis, causing spinal cord compression

Thus, while epidurals were viewed as the gold standard for major open pelvic abdominal and thoracic surgery, they also have numerous disadvantages as shown in Table 14.4.

Epidural failure rates are complex and variable and depend on many factors, such as the definition of failure, the site of surgery, the dosage and volume of drugs administered, as well as problems surrounding their insertion. The range of quoted epidural failure rates vary widely between 13% and 47%, with a large study describing an incidence of 32% for thoracic epidurals and 27% for lumbar epidural [21]. While the situation may be rectified (e.g., by re-siting or adding adjuvants, such as epidural diamorphine), a failed epidural leaves the patient in pain and may restrict other options of analgesia too (such as systemic opioids) as these drugs cannot be co-administered if the patient is receiving epidural opioids.

Another key area is hypotension, which is related to the sympathectomy from neuraxial block. This may be compounded by other factors such as hypovolemia, antihypertensive medication, and postoperative vasoplegia. Historically these patients received copious—even excessive—volumes of intravenous fluids to combat hypotension. This may result in large volumes of fluid administered yet with little effect on blood pressure while causing edema. For many patients the margin of error of fluid overload may be small—e.g., 2.5–3 L—and there is general acceptance that near-zero fluid balance (and weight gain) should be the target [22] with even 1 L of weight gain associated with both increased symptoms (16%) and complications (32%) [23] and increased length of stay of 1 day [24]. A more logical and effective approach is to restore vascular tone with vasoactive drugs (e.g., phenylephrine or noradrenaline), the safe

administration of which requires the patient to be cared for on a high dependency or intensive care unit (ICU), often with intra-arterial blood pressure monitoring [20].

Reduced mobility with epidural analgesia may result from low (lumbar) epidurals and high volumes/high concentrations of local anesthetic mixtures, which will block both motor and proprioception nerve fibers. Early mobilization is key postoperatively, and the combination of a patient having leg weakness and being attached to a bag of IV fluid will significantly impact on the success of any ERAS program.

In addition, although epidurals are widely viewed as relatively safe, permanent neurological damage can occur, due to either vertebral canal hematoma, abscess, or direct trauma. The NAP3 study highlighted the risks associated with postoperative epidurals having an incidence of permanent neurological harm estimated between 1:5700 and 1:12,200 [25].

Thus, while epidurals have a sound theoretical basis in reducing the metabolic responses to surgery and historically were a cornerstone for ERAS in its early days with primarily open surgical techniques, the advent of MIS and appreciation of the side effects of epidurals have led to a significant decline in their use.

Stress Response Modification: Modern Approach

So, what can the anesthesiologist do to reduce surgical stress? In true ERAS fashion, there is no single answer but a number of multimodal approaches that the anesthesiologist can employ to minimize surgical stress and the physiological disruption that in turn prevents early recovery, hospital discharge, and a return to functional normality.

Preoperatively

Hydration and Nutrition: Carbohydrate Loading

A generation ago, patients very often arrived to the operating room theater both dehydrated and starved for many hours. While there were historical reasons for this—it was felt that this minimized gastric volume and in turn the risk of pulmonary aspiration of gastric contents—a number of studies from the 1980s showed that withholding oral fluids was not only unnecessary but that drinking clear fluids up to 2 hours preoperatively had no deleterious effect on both the volume and the pH of gastric contents [26, 27]. However, this did not address the consequences of withholding calories to patients, who, even if they were not dehydrated, were often catabolic and ketotic prior to surgery itself. Given the further major metabolic changes occurring following the surgery, a logical approach was to ensure metabolic homeostasis by feeding and thus prepare patients for these changes. Early studies examining preoperative intravenous glucose were superseded by oral carbohydrates administration, both of which produced dramatic metabolic improvements: There were a reduction in postoperative IR, reduction in protein loss with improved muscle function, and reduced length of hospital stay compared to controls. This area has recently been reviewed [28–31] (see Chap. 4).

There have been several meta-analyses/reviews of the outcomes of carbohydrate loading. Awad et al. showed reduction of postoperative IR and a small but significant reduction in LOS for abdominal surgery of 1.08 days (95% confidence interval [CI] 1.87–0.29 days), although there was no benefit for surgeries with an expected LOS of less than 2 days nor in patients undergoing orthopedic surgery [32]. They also confirmed the reduction of postoperative IR, but no changes in hospital complications. A later review published in the Cochrane Database demonstrated a smaller reduction in overall LOS (0.3 days, 95% CI 0.56–0.04 days) but with a highly significant reduction in LOS of 1.6 days for patients undergoing abdominal surgery together with a shorter time for passage of flatus (0.39 days, 95% CI 0.70–0.07 days) with again a reduction in IR and no effect on complications [33]. A very recent study confirmed the benefits of carbohydrate loading in terms of LOS compared to fasting controls, but was unable to show this difference for those patients who received water or placebo [34]. While some have criticized the methodology of this review, overall there is evidence of reduction in LOS from carbohydrate loading (although its exact effect on LOS may be debated). Moreover there is no doubt that it is an intervention that produces marked and reproducible modifications on the stress response markers of major surgery. In addition, early oral nutrition will help prevent catabolism postoperatively.

Prewarming

The concept of prevention of hypothermia is covered below. The use of prewarming is growing too and, while not always to achieve from a practical perspective, has been shown to result in significantly higher temperatures perioperatively (see Chap. 17).

Management of Anxiety

Preoperative anxiety may magnify the stress response, and whereas the conventional use of anxiolytics has greatly declined, other approaches such as preoperative preparation, minimizing fasting, and administering carbohydrates will all reduce anxiety and improve patient comfort.

Intraoperative Management

The anesthesiologist's role in intraoperative management is fundamental. Some of these areas can be divided into

protocolized care bundles and represent a standard of care undertaken in every patient. Many are simple and merely reflect good anesthetic practice but if not undertaken may significantly magnify the stress response. These include key practices described below.

Appropriate Intravenous Antibiotics

Perioperative infections, depending on their magnitude, have the potential to cause marked organ dysfunction.

Avoidance of Hypothermia

Measurement of temperature and active avoidance of hypothermia (<36 °C) is fundamental anesthetic practice. Even mild hypothermia (with a median temperature of 35.6 °C) blood loss was increased by 16% and blood transfusion rate by 22%. Not only will hypothermia again magnify aspects of the stress response (e.g., excess catecholamines) but cause a number of pathophysiological sequelae including vasoconstriction, increased afterload, myocardial ischemia and cardiac arrhythmias, surgical site infection, and coagulopathy, all with the potential to increase hospital stay. More recently the concept of prewarming has been popularized too as another method to prevent hypothermia (see Chap. 17).

Depth of Anesthesia Monitoring

For elderly patients in particular, postoperative inflammatory changes in the brain may predispose to both postoperative cognitive dysfunction and postoperative delirium, and the targeted use of depth of anesthesia monitoring has been advocated to keep anesthetic depth to a safe minimum to reduce these unwanted effects [35].

Monitoring of Neuromuscular Block (NMB)

The quantitative monitoring of, and proven reversal from, NMB is essential for patients to reduce risks of postoperative pulmonary complications, which will magnify the stress response [36].

Intravenous Fluid Management

Fluid management remains probably the most widely covered topic in the literature but remains a contentious area of intraoperative care, and a full debate is outside the scope of this chapter (see Chap. 18). While both anesthesiologists and intensivists may debate some areas of fluid management, there are nevertheless some areas that have general agreement:

- Poor fluid administration can be disastrous for ERAS patients and will increase both the inflammatory (as measured by IL-6) [37] and metabolic markers of major surgery.
- Both too little fluid (causing a reduction in cardiac output) and excess fluid excess (causing edema particularly to the lungs but also to an anastomosis) will ultimately impair tissue oxygenation, with an increase in complications, cost, and LOS [23, 24].
- Many support the use of individualized fluid therapy (e.g., goal-directed fluid therapy [GDFT]) to manage fluids, especially for higher-risk surgeries and/or patients.
- There is nevertheless a large range in IV fluid regimens administered for similar surgery that is personnel-dependent [38, 39].
- IV fluid management has changed due to other changes in perioperative care. e.g., the use of carbohydrate loading, early resumption of postoperative oral fluids (so less IV fluids required), MIS surgery (so less bowel handling and fluid shifts), and the appreciation that permissive intraoperative [40] and postoperative oliguria are acceptable to a degree (so less chasing of urine output with IV fluids).
- As a result of changes embedded in ERAS programs, GDFT now has less of an impact in improving outcomes (historically reduced morbidity, LOS, swifter return of bowel function) to perhaps just improving outcomes in high-risk patients who require ICU [41].

Areas that are unresolved include:

- Applying conventional fluid management for MIS is contentious as the technique (e.g., pneumoperitoneum) will make GDFT difficult to interpret with generally lower oxygen deliveries accepted [42].
- The optimal cardiac output monitors/goals, duration of therapy, and optimal markers, e.g., lactate and $ScvO_2$.

Thus, intravenous fluid management is a key area that may substantially add to perioperative stress if poorly executed.

Analgesia

The provision of perioperative analgesia is at the heart of clinical anesthesiology. Poorly executed analgesic programs will exacerbate the stress of surgery [5] and lead to other undesirable effects such as poor mobilization, respiratory effort, prolonged bed rest, and increased length of stay. As discussed above, while there are some potent analgesic modifiers of surgical stress available, they need to be viewed within the context of the aims of modern ERAS programs. Thus, while in particular epidural anesthesia can dramatically obtund the endocrine and metabolic response to say knee or hip surgery, it is not *rasion d'etre* of ERAS anesthesiologists. As we have seen above, the side effects of both high-dose fentanyl and TEA have led to their decline, in spite of their beneficial effects on the stress response, with remifentanil offering merely transient effects.

So a balance has to be struck: good analgesia, stress response modification, and a satisfactory side effect profile.

Table 14.5 Adverse effects of opioids

Adverse effects of opioids
Postoperative nausea and vomiting
Constipation and ileus
Respiratory depression and cough suppression
Dysphoria and confusion
Urinary retention
Acute tolerance and hyperalgesia
Long-term dependence

Opioids are seen as the gold standard for pain relief after major surgery, but for the last 25 years, the understanding is that their numerous side effects (Table 14.5) have led to strategies to limit their use, which embodies Kehlet's concept of multimodal, opioid-sparing analgesia [13].

Broadly, analgesia may be classified under three major headings:

- Systemic analgesics
- Local anesthetics
- Non-analgesic methods
  - Acupuncture
  - TENS (transcutaneous electrical nerve stimulation)
  - Hypnosis

The last methods will not be considered further here.

Systemic Analgesics

These include opioids, paracetamol, and the anti-inflammatory drugs and various more recently popularized adjuvants, such as anticonvulsants, lidocaine, etc. Opioids have been discussed, and while many patients require opioids, within ERAS, opioid-sparing is practiced so that they are titrated to a minimal dose for the shortest period.

Given the central role that inflammation plays within the classical stress response, it is logical that both the non-steroidal anti-inflammatory drugs (NSAIDs) and steroids occupy a key role. NSAIDs form a cornerstone of analgesic management, with significant opioid-sparing. There are a number of well-documented side effects—in particular, upper gastrointestinal (GI) perforation and hemorrhage, reduced glomerular filtration rate (GFR) leading to acute kidney injury (AKI), bleeding, asthma, and thrombotic events. More recently the potential link between NSAIDs and both anastomotic breakdown and cancer recurrence has been highlighted [43].

But what is their role in reducing the inflammatory response of surgical stress? NSAIDs work inhibiting cyclooxygenase (COX), which produces prostaglandin H2 (PGH-2) from arachidonic acid. PGH-2 is a metabolite converted into prostanoids (prostaglandins, prostacyclins, and thromboxanes), which play a central role in inflammation, coagulation, and vascular permeability and tone. There are two basic isoforms of cyclooxygenase inhibitors: COX-1 and COX-2. The latter have a different side effect profile, as they target gastrointestinal cyclooxygenase rather less and may offer lower incidences of gastrointestinal ulceration compared with COX-1 inhibitors, although studies have also suggested higher risk of cardiac events in higher-risk patients given COX-2 inhibitors [44].

There is a complex interplay between prostanoids, which play a key role in inflammation, and the resultant commonly measured cytokines such as interleukins, CRP, etc. There is little data in this area, but in cardiac surgical patients, intraoperative parecoxib attenuated the systemic inflammatory response associated with CPB during cardiac surgery with a marked reduction in concentration of IL-6 and IL-8, with peak concentrations of anti-inflammatory cytokine IL-10 higher than in the parecoxib group [45]. Another study showed a significant reduction in IL-6 and CRP following parecoxib following percutaneous nephrolithotomy. Pooling both the theory and data collected, NSAIDs will certainly have a major impact on reducing the inflammatory limb of the stress response [46].

The role of preoperative glucocorticoids is very topical and has also been extensively investigated. While small doses of dexamethasone are regularly administered for PONV prophylaxis (see Chap. 21) without ill effect (including significant hyperglycemia), the successful use of much larger doses of glucocorticoids (both dexamethasone and methylprednisolone) has been described. With the appreciation that a marked inflammatory response may have contribute to both postoperative pain and organ dysfunction, higher doses of glucocorticoids were postulated to be able to modify this effect, although there was the potential concern for complications due to the steroids such as healing, hyperglycemia, and infections.

On the face of it, there may seem to be a paradox between trying to reduce the hormonal response to surgery (such as reduced cortisol) and the co-administration of large amounts of steroids. However, early studies in abdominal surgery demonstrated that high-dose methylprednisolone (30 mg/kg) reduced IL-6, IL-8, and CRP, with a more transient reduction in TNF alpha [47], with a later meta-analysis confirming both its efficacy and safety [48].

However, it is the inflammatory response in orthopedic surgery in particular that has been studied extensively. Whereas measured hormonal markers (catecholamine levels) did not appear to have any predictive value on the early postoperative course, inflammatory markers were more useful, with IL-6 concentration a unique predictor for time to walk 10 and 25 meters and CRP concentrations a unique predictor for pain on discharge from hospital [49]. The magnitude of the inflammatory stress response and its link to functional recovery has been a key driver for the administration

of methylprednisolone for patients undergoing hip and knee arthroplasty, demonstrating a marked reduction in both pain and cytokines levels without any apparent increase in complications [50, 51], and will no doubt stimulate further research in this area.

Intravenous lidocaine is an agent that has been used for many years and known to play a useful analgesic role, providing opioid-sparing analgesia, a shortened ileus, and interestingly an anti-inflammatory effect too, superior in some respects to traditional anti-inflammatory drugs, both NSAIDs and steroids [52]. Indeed, some of the benefits of effects of epidural lidocaine may be explained by a systemic effect, as plasma concentrations of the two are similar [53]. The sustained anti-inflammatory effects of lidocaine are poorly understood as they considerably exceed the half-life of the drug, but one mechanism seems to relate to the ability of lidocaine to prevent priming of polymorphonuclear leukocytes, effectively disabling them from initiating their usual release of cytokines and reactive oxygen species [53], via an inhibition of G protein signaling [54]. However, although it has a marked anti-inflammatory effect, the place of IV lidocaine is still not certain, with recent reviews questioning its effects on pain scores, return of GI function, PONV, and opioid consumption due to generally poor quality of published data [55, 56]. In spite of this, there is evidence for procedure-specific effects (reducing pain and return of bowel function in abdominal procedures) and improving functional outcome too in other procedures (spine, prostate, and thoracic surgery, but not in total abdominal hysterectomy, total hip arthroplasty, or renal surgery) [53]. Overall it is an intriguing modifier of the inflammatory response, but its true place remains to be identified.

Local Anesthetics

The administration of local anesthetics (LA) within the pain pathway—from surgical site to neuraxial block—has been reviewed in the early part of this chapter. In essence, while TEA with LA remains the gold standard for open cavity surgery, as surgical techniques have changed to MIS, the risk-benefit has changed favoring other analgesic methods. Spinal anesthesia appears to offer a logical analgesic compromise by still having an albeit limited effect on the stress response vide infra [17], but as a single shot technique would have its side effects (such as hypotension and poor mobilization) also limited.

Experiences from a range of both open surgery (e.g., joint arthroplasty, cesarean delivery) and MIS surgery (laparoscopic and robotic surgery for bowel, gynecology, and urology) have provided support for this technique. The stress response to spinals has not been extensively studied, although it was shown that a spinal anesthetic significantly reduced (3 hours) glucose and cortisol levels, with no significant differences in insulin, interleukins, interferon gamma, TNF alpha, or vascular endothelial growth factor (VEGF) [17], which is entirely logical given the transient nature of the spinal anesthesia on the neuroendocrine pathway. In addition, the success of spinal anesthesia for laparoscopic colorectal surgery enabled the first 23-hour stay colectomy paper [57] as well as showing that TEA in this group of patients prolonged LOS, reduced mobilization, and increased in fluid requirements [17].

However, there have been trends in moving away from neuraxial blockade completely in open surgery and using abdominal wall blocks (e.g., rectus sheath catheters, transversus abdominis plane [TAP] block or LA into the wound edges), either as an injection or by infusion, with good success for postoperative pain relief. There is very little evidence on the impact of these more "peripherally" sited blocks on the stress response. Paravertebral blocks effectively obtund neuroendocrine activation as measured by cortisol and glucose responses [58, 59]. There is also some blunting of these responses with TAP blocks in children undergoing hernia repair [60], with predictably very little effect on the interleukin response when rectus sheath block was performed [61], as inflammatory activation is not neurally mediated.

Conclusion

In summary, there is much that the anesthesiologist can do to reduce surgical stress. Good protocolized anesthesia and attention to nutrition, fluid management, blood loss, and avoidance of hypothermia are key. Analgesia can play a major role with consideration given to neuraxial block where appropriate. The use of systemic analgesic adjuvants to control inflammation and its sequelae is key—NSAIDS, steroids, and others (e.g., IV lidocaine) are also described. Reduction in surgical stress will be minimized by early drinking, eating, and mobilization [62], and any strategies that permit that will very probably reduce the stress response pari passu.

Future developments may take us in a variety of directions: specific anti-cytokine drugs or perhaps using genomic data to predict the type of patients and surgeries in whom a specific modification of surgical stress can be linked to improved outcome.

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Analgesia During Surgery (Medications)

15

Hans D. de Boer

Introduction

The concept of balanced general anesthesia, which consisted of unconsciousness, analgesia, and relaxation, the components of the "triad of anesthesia," was first described by Cecil Gray in 1946 and was a big step forward in anesthesia and perioperative care [1]. Before this change in conceptual strategy, general anesthesia was performed using high doses of hypnotics or inhalation gases, which resulted in hemodynamic suppression and dangerous deep levels of anesthesia with concomitant morbidity and mortality [2, 3]. However, even with these high doses of anesthetic drugs, suppression of noxious stimuli was difficult. Therefore, the introduction of balanced anesthesia using different drugs to reach each desired goal was the first step in the development of multimodal analgesic and general anesthesia techniques. Introduction of synthetic opioids in general anesthesia resulted in more hemodynamic stability and less histamine release, which improved the balanced anesthesia technique [4]. For a long time, high-dose opioids were regarded as the cornerstone of hemodynamic stability and perioperative analgesia, helping improve anesthesia and surgical outcomes. However, high-dose opioids during anesthesia alone have many postoperative side effects, such as postoperative nausea and vomiting (PONV), respiratory depression, delirium, hyperalgesia, sedative effects, and delayed recovery [5]. In modern anesthesia, besides opioids, additional antinociception strategies such as neuraxial blockade, locoregional techniques, and non-opioid additive drugs are available to achieve this goal. Intraoperative nociception management is essential to enhanced recovery after surgery (ERAS) pathways in order to anticipate and reduce postoperative side effects of anesthesia drugs in relation to early recovery after surgery [6]. In this chapter the intraoperative management of analgesia during surgery is outlined and discussed. Neuraxial or locoregional techniques will be discussed in Chap. 16.

Pain Pathways in the Context of Analgesia During Anesthesia

The classical components of the triad of anesthesia—hypnosis, muscle relaxation, and analgesia—are part of the concept of balanced anesthesia. Pain pathways within the context of analgesia during anesthesia and postoperative pain management need to be evaluated. In fact, antinociceptive strategies should ideally be included in the intraoperative period already and be a continuum postoperatively in order to have adequate postoperative pain relief and improved outcome [7].

In order to optimize and understand intraoperative analgesia management, a more detailed overview on pain physiology and pain pathways is important. Nociception induced by surgery is a complex and multifactorial process [8, 9]. The nociceptive system consists of the nociceptors and the ascending and descending nociceptive pathways [8–10]. The nociceptors are nerve cell endings located in viscera and peripheral tissue that initiate nociception (primary pain). After surgical incision, tissue damage leads to cell disruption and a release of a variety of chemical mediators such as cytokines, potassium, adenosine, bradykinin, and many others [11, 12]. This first step leads to activation and sensitization (peripheral sensitization) of peripheral nociceptors to mechanical stimuli [13]. These activated primary afferent neurons, part of the peripheral nervous system, have cell bodies located in the dorsal root ganglia of the spinal cord. The ascending nociceptive pathway sends nociceptive stimuli from the peripheral area up to the spinal cord to the brainstem (midbrain and medulla), the amygdala, the thalamus, and the sensory cortices [13].

The descending nociceptive pathway modulates stimuli from supraspinal levels (sensory cortex) and projects to the hypothalamus and amygdala and synapses in specific areas

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in the medulla. This pathway is activated by ascending nociceptive pathways and is able to upregulate or downregulate nociceptive information. As a result of derangements, which can occur in both ascending and descending nociceptive pathways at any and all levels, chronic pain can be generated after initially acute pain post-surgery [13].

After local tissue injury as a result of the incision, many different cascades are activated that lead to the release of neurotransmitters, stress hormones, catecholamines, inflammation products, and many other nociceptive-related products. This leads to a disbalance in sympathetic and parasympathetic outflow, neuroinflammation, and a situation of whole end-organ dysfunction [11, 12]. Intraoperative nociception is a complex and multifactorial process that cannot easily be modulated by the application of the classical triad of anesthesia: hypnosis, muscle relaxation, and analgesia. As understood from the aforementioned nociceptive pathways, multiple target areas can be identified upon which antinociception can be applied in order to block or mitigate nociceptive signaling processing and transmission. The scientific rationale for a multimodal or more precise multitarget analgesia approach is based on the multifactorial nature and complexity of the nociceptive pathways that are activated due to surgery [11–13]. Multimodal or multitarget analgesia to control nociception with different classes of drugs will be the future in anesthesia and ERAS pathways in order to prevent nociceptive stimuli affecting the central system, reduce surgical stress, and prevent postoperative pain developing (Table 15.1) [11–13]. In the next section, the intraoperative multimodal analgesia management is discussed.

Intraoperative Multimodal Analgesia Management

Opioid Analgesics

Opioids have been the cornerstone for perioperative analgesia for decades. In 1932 pethidine was synthesized and was the first synthetic opioid used during anesthesia in 1949 [3]. In the early 1960s, fentanyl was introduced in clinical anesthesia allowing for better cardiovascular stability and to improve balanced anesthesia [4]. In the last 50 years, several synthetic opioids were developed, which have been used or are still in use in anesthesia practice [13].

Opioids can be classified as naturally occurring (morphine, codeine, or papaverine), semisynthetic (heroine), or synthetic (e.g., phenylpiperidine series: meperidine, fentanyl, sufentanil, alfentanil, and remifentanil) [13]. Today, the most commonly used perioperative opioids are (among others) fentanyl, sufentanil, alfentanil, and remifentanil [13].

The mechanism of action of opioids is well understood, and opioids bind to several classes of opioid receptors in many areas (central and peripheral) in the human body, but mainly in the brainstem and spinal cord [13, 14]. Binding to these opioid receptors results in a direct disruption (inhibition) of ascending transmission of nociceptive information from the spinal cord dorsal horn and to activate pain control circuits that descend from the midbrain, through the rostral ventromedial medulla, to the spinal cord dorsal horn [13, 14]. The inhibition is achieved by lowering the conductance of voltage-gated calcium channels and opening the potassium channels, which is described in the previous section [13].

Table 15.1 Antinociceptive drugs for multimodal strategies

Antinociceptive drugs	Mechanism of action	Comments
Paracetamol	Unknown. Possible inhibition (central) of COX-mediated prostaglandin production	High-quality evidence of effectiveness when given intravenously
NSAIDs	Inhibition of COX enzymes to reduce inflammatory cytokines and chemokines	Potential issues such as renal dysfunction
Opioids	Opioids bind to several classes of opioid receptors in many areas (central and peripheral) in the human body	In multimodal antinociceptive strategies, opioids have a less important position Potential issues such as OIH, side effects, and opioid addiction
Ketamine	Acts on multiple receptors: NMDA, opioid, and monoaminergic receptors Main mechanism of action: antagonist for the NMDA receptors	Opioid-sparing effects and improved analgesia. In combination with magnesium, increased cardiovascular stability
Magnesium	Antagonist for NMDA receptors	Potential risk in patients with AV conduction diseases and interaction with muscle relaxation
Lidocaine	Binds to and blocks the sodium channel	Moderate-quality evidence of reduced pain Opioid-reducing
Beta-blocker	The exact mechanism of action is unknown	Data available that beta-blockers decrease opioid consumption and reduce pain scores
Dexmedetomidine/ clonidine	α(alpha)2 adrenergic agonist	Sedative effects and hypotension can occur
Dexamethasone	Reduction of the inflammatory response to surgery	Consider effects on immune function

COX cyclooxygenase, *NMDA* N-methyl-D-aspartate, *NSAIDs* non-steroidal anti-inflammatory drugs, *OIH* opioid-induced hyperalgesia

However, the classic μ(mu)-receptor agonists (opioids) cannot be regarded as specific for pain circuits or blocking the nociceptive stimulus. Therefore, these μ(mu)-receptor agonists (opioids) are responsible for many unwanted side effects, such as nausea and vomiting, ileus, urinary retention, ventilator depression, hyperalgesia, and the more recently described opioid addiction, which is pandemic in many parts of the world [13, 15].

Opioid analgesics are the oldest kind of analgesics used during classic balanced anesthesia and thought to be the best solution to modulate and block the sympathetic activation and parasympathetic inactivation as result of surgery [11, 13]. The use of short-acting general anesthetic drugs in an opioid-sparing ERAS pathway allows rapid awakening with minimal residual effects. When indicated, short-acting opioids such as fentanyl, alfentanil, sufentanil, or remifentanil infusions—if opioids are required—minimize residual effects at the end of anesthesia [7, 11–13]. However, intraoperative nociception through the administration of non-opioid analgesics versus opioid analgesics will be the future in order to achieve minimal postoperative residual effects as well as side effects and improve outcomes. In the next section, non-opioid drug strategies to understand multimodal analgesia will be discussed.

Non-opioid Additives Within the Context of Multimodal Anesthesia

Lidocaine

Lidocaine (2-(diethylamino)-N-(2,6-dimethylphenyl)acetamide) is an amino-amide local anesthetic drug, which was first synthesized in 1934 [16]. Lidocaine is widely used in clinical anesthesia and has analgesic, anti-hyperalgesic, and anti-inflammatory effects [16].

Lidocaine is a weak base that binds to plasma protein (e.g., albumin) and undergoes hepatic metabolism up to 90%, which results in some active metabolites [16]. Lidocaine is eliminated by the kidney [16]. The half-life of lidocaine is around 1.5–2 hours when a bolus is administered, while the half-life could be increased by 3 hours when administrated intravenously [16]. When lidocaine is administrated for longer than 24 hours, accumulation takes place, and therefore the intravenous doses should be decreased accordingly. Plasma lidocaine concentrations achieved are similar to those when running an epidural infusion (approximately 1 μ[mu]M) [17]. Toxicity is related to the plasma concentration and appears to be rare, but monitoring in the postoperative period is important [16, 17].

The antinociceptive effects of lidocaine are accomplished by binding to the sodium channels, thereby blocking the voltage-gated sodium influx required to induce and sustain action potentials [16, 17]. Blocking the voltage-gated sodium channels is most likely not the only underlying mechanism of action, which is complex and not fully understood. Another possible mechanism contributing to antinociception is the anti-inflammatory property of lidocaine, which results in a reduction in the release of pro-inflammatory cytokines (interleukine-1β[beta], TNF-α[alpha]) by reducing neutrophil activation [17]. More research in this field is needed in order to understand this interesting area of antinociception of lidocaine.

Intravenous lidocaine has been investigated extensively in the recent years [17]. Many well-designed clinical trials and meta-analyses have confirmed the efficacy of intravenous lidocaine in terms of significant pain reduction and reduction in opioid consumption within the first 24 hours postoperatively, although some have questioned the quality of the evidence [16, 17]. Furthermore, intravenous lidocaine administrated in major abdominal surgery showed reduction in postoperative ileus, time to the first bowel movements, and postoperative nausea and vomiting [7, 16–18]. In a recent clinical comparison of intravenous and epidural local anesthetic for major abdominal surgery, no significant difference between both techniques could be found [16–18]. The efficacy of intravenous lidocaine was also confirmed in a recent review that evaluated the neuroinflammation response in perioperative and chronic neuropathic pain [16, 18].

The recommended dose of lidocaine during the perioperative period is 1–2 mg/kg as a bolus dose. This can be followed by a continuous infusion of 1–2 mg/kg/h lidocaine administered for 24–48 hours postoperatively, which is usually recommended [16, 17]. However, in recent meta-analyses, the length and doses of continuous intravenous administration of lidocaine are discussed. In long surgical procedures, the dose of lidocaine by continuous infusion might need to be reduced progressively, 50% every 6 hours, as the period of the surgical procedure is longer [17]. This idea is based on the half-life of lidocaine and its metabolites, as described previously. The length of lidocaine continuous infusion varies in literature, but it is now recommended to stop this just before discharge to the ward as there is no benefit in prolonged administration beyond the recovery room [17]. Lidocaine is an effective drug additive and has clear analgesic benefits and enhances recovery after surgery, thereby improving outcome.

Ketamine

Ketamine, a phencyclidine derivative, was first used in humans in 1965 and released on the market in 1970; it is still used in clinical anesthesia, emergency medicine, and pain medicine [19]. Nowadays, the S(+)-isomer of ketamine (ketanest) is used in clinical practice, which is 3–4 times more potent as an analgesic. Furthermore, this S-isomer has a rapid onset (1–2 minutes), a relatively rapid offset even after

intravenous administration of several hours, fewer psychomimetic side effects, and a faster clearance (elimination half-life 4–6 hours, clearance 12–17 ml/kg/min) [19].

Ketamine acts upon multiple receptors, such as N-methyl-D-aspartate (NMDA), opioid, and monoaminergic receptors [13, 19]. However the most important mechanism of action of ketamine is acting as an antagonist for the NMDA glutamate receptors located on peripheral afferent nociceptive neurons synapsed in the dorsal horn of the spinal cord. Inhibition of these receptors results in a reduction of input to the gamma-aminobutyric acid-ergic (GABAergic) system, which leads to excitatory activity in the limbic system and cortex, which leads to unconsciousness and antinociception at the spinal cord level due to inhibition of acetylcholine release [13]. However, the analgesic effects of ketamine may arise from multiple pathways and the opioid μ(mu)-receptor activity of the S-isomer of ketamine may account for analgesic effects as well. Ketamine affects the connectivity in brain areas resulting in decreased connectivity in the areas responsible for the perception and affective processing of pain.

Ketamine is now mainly used for antinociception in the perioperative setting or in pain medicine [13]. It usually does not have cardiorespiratory effects and has potential effects to preserve the autonomic reflexes and cardiac function. Ketamine has shown positive results in opioid tolerance and hyperalgesia [13, 18, 19]. Ketamine administered in small doses decreased the postoperative analgesic consumption by 33%. In several meta-analyses it was shown that ketamine in doses up to 60 mg perioperatively resulted in an overall decrease in opioid consumption, improved postoperative analgesia, and a decrease in opioid-induced side effects such as postoperative nausea and vomiting, postoperative ileus, and urinary retention [5]. It has been shown that the action of the combination of ketamine and magnesium could be complementary during general anesthesia regarding antinociception and cardiovascular stability. Ketamine can be administered as a bolus dose at induction of 0.5–2 mg/kg or maintained by continuous infusion in a rate of 30–90 μ(mu) g/kg/min [19].

Ketamine in low doses is an important drug additive in general anesthesia in ERAS pathways and shows benefits and improved outcome regarding a decreased opioid intake and lower postoperative pain scores, which enables early mobilization.

Alpha-2 Agonists

In the early 1960s, the first alpha-2 (adrenergic) agonist, clonidine, was developed and successfully introduced as an antihypertensive drug [20]. However, it was only during the 1980s that clonidine was first used in anesthesia in order to reduce sedative and analgesic requirements [18, 20]. In the late 1980s, a more specific alpha-2 (adrenergic) agonist, dexmedetomidine (elimination half-life 2–3 hours, clearance 10–30 ml/kg/min), was introduced in anesthesia in veterinary medicine, which showed even more potent effects than clonidine [13, 18, 20]. Alpha-2 agonists such as clonidine and dexmedetomidine belong to the family of imidazolines and bind to both imidazolines and adrenergic receptors [13]. Binding to the alpha-2 adrenergic receptor results in an activation of inhibitory G-proteins and a decrease in cyclic adenosine monophasphate (cAMP) [18, 20]. The effect of alpha-2 agonists is sympatholysis resulting in sedation and low blood pressure, which is caused by binding to the alpha-2a receptors. Binding to the alpha-2b receptors will result in a transitory increase in blood pressure caused by direct vasoconstriction [13, 18, 20]. Alpha-2 receptors are located in the central nervous system (CNS) in the noradrenergic nuclei (locus coeruleus) and are part of the neural pathways of sleep. Alpha-2 adrenergic receptor agonists, such as dexmedetomidine, induce sedation in lower doses, but with increasing dose, they may induce an anesthesia state [18, 20].

Analgesia induced by alpha-2 agonists is related to opioid receptors, and the most important site of action is on the spinal level [13, 18, 20]. In healthy volunteers, dexmedetomidine showed comparable analgesic effects to that of opioids. In several studies, dexmedetomidine showed the opioid-sparing effects up to 24 hours postoperatively [13, 18, 20]. Moreover, the frequency and intensity of postoperative pain were lower. Furthermore, there is an indication that alpha-2 agonists reduced postoperative nausea and vomiting, but the mechanism behind this is not clear [20].

Alpha-2 agonists, in particular clonidine, are associated with an increased risk of hypotension and bradycardia [18, 20]. However, no effects on myocardial infarction in patients under non-cardiac surgery were shown. Another concern was the sedation effect of dexmedetomidine postoperatively, which possibly delayed the recovery time. However, when dexmedetomidine was administered perioperatively, a reduction in time to spontaneous ventilation and tracheal extubation were found. Furthermore, a reduction in recovery time was observed [13, 18, 20].

Typical doses of dexmedetomidine administration for sedation and analgesia are 0.5–1.0 μ(mu)g/kg as a loading dose and a maintenance infusion of 0.2–0.7 μ(mu)g/kg/min [20]. Clonidine is mainly used as a bolus dose of 150–300 μ(mu)g at induction of anesthesia [13, 20]. However, as dexmedetomidine is more target specific and can be titrated to effect, it is the preferred drug as an adjunct during anesthesia.

Alpha-2 agonists are interesting drug additives that have analgesic effects and therefore opioid-sparing effects. When used in multimodal anesthesia strategies, alpha-2 agonists showed benefits in ERAS pathways in a variety of surgical procedures.

Magnesium

Magnesium is an important cation involved in many physiological processes in humans, which regulates voltage-dependent Na^+, K^+, and Ca^{2+} channels [13, 18, 19]. Therefore, magnesium is an ideal antiarrhythmic drug, which prolongs the AV-node conduction leading to stable heart rates and is used frequently in cardiology [18]. Furthermore, magnesium is used in obstetrics to treat hypertensive crisis in preeclampsia and mediated by blocking calcium channels [18].

In clinical anesthesia and pain medicine, magnesium has shown antinociceptive effects. Magnesium blocks the NMDA receptors and inhibits the glutamatergic synapses, leading to antinociceptive effects—especially in combination with ketamine as this combination of drugs provides improved postoperative analgesia [18, 19]. Furthermore, magnesium alone potentiates the effects of hypnotics and reduces the hemodynamic variability during surgery and reduces the opioid consumption postoperatively.

The induction dose of magnesium when multimodal anesthesia is applied is up to 40 mg/kg and can be continued by intravenous administration of 8 mg/kg/h, which significantly reduces the intraoperative and postoperative fentanyl requirement [19]. It should be recognized that high doses of magnesium may lead to decreased AV conduction, heart block, and possibly cardiac arrest [19].

Magnesium is an effective drug additive to general anesthesia, used not only to reduce hemodynamic variability during surgery but also to improve postoperative analgesia.

Beta-Blockers

Beta-adrenergic blockade is well-known and an important mechanism for reducing morbidity and mortality in patients with hypertension and heart failure [21–24]. Esmolol has been used for these indications, but esmolol has shown opioid-reducing effects and might have effects on nociceptive modulation as well [21–24]. Although esmolol has not shown direct analgesic or anesthetic properties, recent studies suggest that esmolol has antinociceptive and postoperative opioid-sparing effects, but also is associated with a decrease in length of hospital stay [21–24].

The mechanism of action of esmolol remains unclear, and this drug should be used with care as bradycardia and hypotension may occur. However, several hypotheses are suggested regarding its mechanism of action [21–24]. One interesting hypothesis is that esmolol blocks the neuronal inflow into the CNS on the brainstem level. Beta blockade might also regulate hippocampal activity during stress, as increased hippocampal activity is observed during stress imaging [21–24]. Activation of hippocampal beta-adrenergic receptors may play a role in nociception, whereas blockade of these receptors should decrease the contribution of such beta-adrenergic activation to the nociceptive process, leading to less pain and opioid consumption. Beta blockade also decreases, in a dose-dependent manner, the pro-inflammatory cytokine interleukin-6 (IL-6) and C-reactive protein (CRP) release in serum and reduces postoperative pain and opioid consumption. However, the exact mechanism is not clear [21–24].

In a previous study it was shown that beta blockade did not alter the hormonal stress response to surgery, but patients on beta blockade showed improved hemodynamic stability perioperatively and directly postoperatively. Furthermore, these patients needed less fentanyl intraoperatively, had lower pain scores, and required less analgesics in the post-anesthetic care unit (PACU), which resulted in improved recovery after surgery. Another study reported that patients undergoing abdominal total hysterectomy who received esmolol as a bolus dose of 0.5 mg/kg followed by infusion of 0.05 mg/kg/min before anesthesia induction showed a reduction in administration of fentanyl and inhalational anesthetics, a reduction in hemodynamic responses, and a reduction in morphine consumption for the first three postoperative days [21–24].

Beta blockade is an interesting and promising drug additive, which demonstrates a reduction in postoperative pain scores and opioid consumption. However, as data is sparse, more research is needed in order to understand the exact mechanism of action of beta blockade in relation to antinociception.

Dexamethasone

Acute inflammation induced by tissue damage due to surgery is a major factor contributing to the development of postoperative pain. Tissue injury induced by surgical procedure is associated with an increased serum level of pro-inflammatory cytokines such as IL-6, tumor necrosis factor-alpha (TNFα[alpha]), and anti-inflammatory IL-10 [13, 25–27]. Furthermore, the preservation of the monocyte function is affected negatively as reflected by lower levels of human leukocyte antigen-DR (HLA-DR) isotope expression on monocytes [54]. The systemic acute inflammatory reaction and massive release of cytokines are responsible for acute postoperative pain [7, 11, 25–27].

The pain relief properties of dexamethasone are well-known in patients with metastatic bone, visceral, and neuropathic pain [25–27]. Although analgesic mechanism of dexamethasone is still unclear, it seems that a decrease in cyclooxygenase and lipoxygenase production, via inhibition of peripheral phospholipase, might play a key role [25–27].

Dexamethasone is the glucocorticoid of choice as it has less mineralocorticoid effects, has a longer half-life, and is more potent [27]. Many publications have reported the reduction of incidence of postoperative pain, opioid consumption, and postoperative nausea and vomiting [25–27].

Dexamethasone should be dosed 0.1 mg/kg up to 8 mg as a single dose at induction of anesthesia. Higher doses are not recommended as these are associated with an increased blood glucose level during the first 24 hours after bolus injection [27]. The intravenous single-dose dexamethasone

will lead to a decrease in total postoperative consumed analgesic, fatigue, and nausea and vomiting [27].

Dexamethasone is an effective and easy-to-administer drug, and even a single intravenous dose can reduce postoperative pain and opioid consumption.

Conclusion

Pain pathways in the context of analgesia or antinociceptive strategies during anesthesia are very complex. Perioperative analgesia in relation to the postoperative pain management should ideally be included in the intraoperative period already and be a continuum postoperatively in order to have adequate postoperative pain relief and improved outcome. Multimodal analgesia strategies to control nociception intraoperatively with different classes of drugs will be the future in anesthesia and ERAS pathways in order to prevent nociceptive stimuli affecting the central system, reduce surgical stress, and prevent postoperative pain developing. Intraoperative multimodal analgesia, including opioid and non-opioid additives within the context of multimodal anesthesia management, is a key component of an ERAS pathway (see Fig. 15.1).

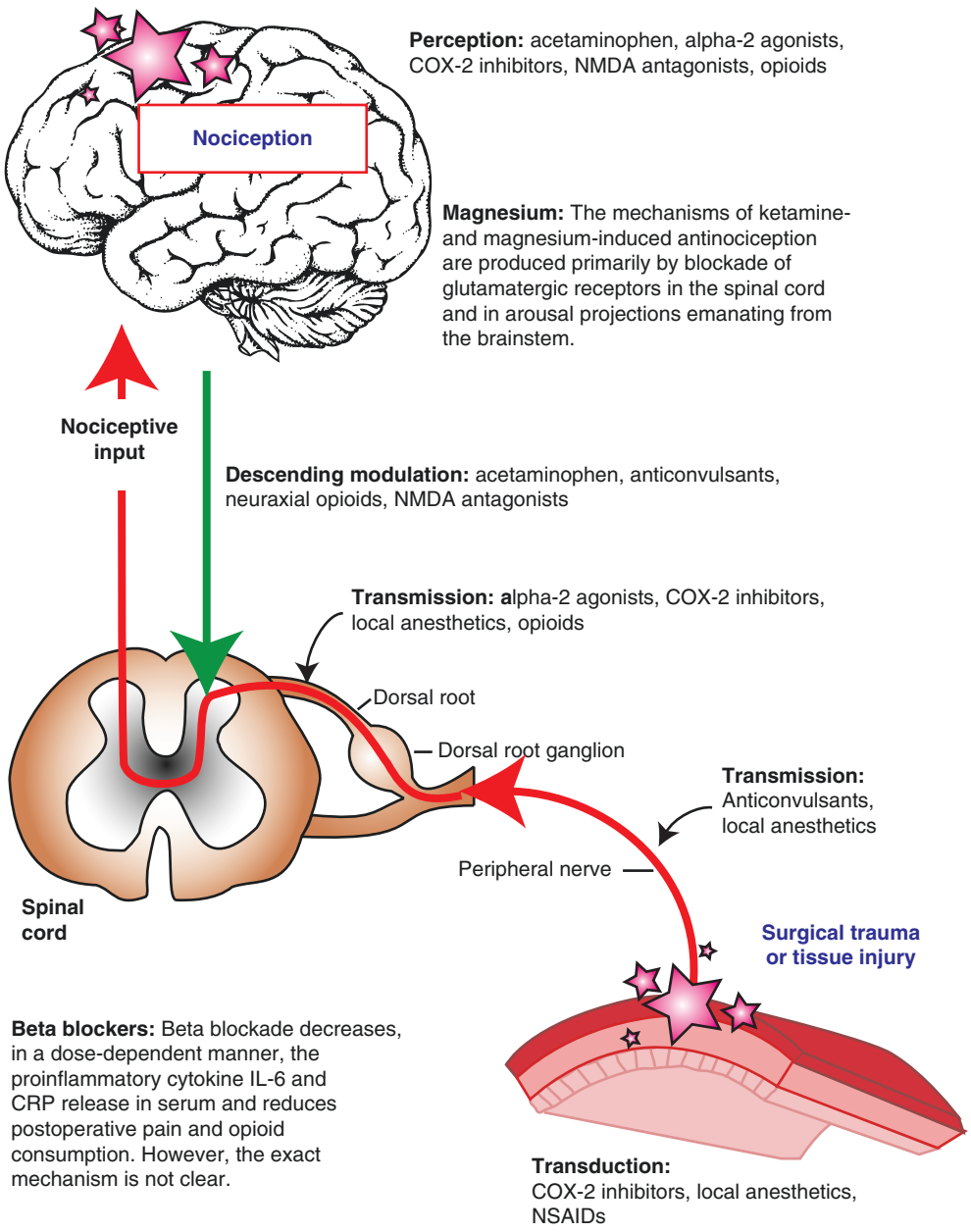

Fig. 15.1 Multimodal analgesia mode of action

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Regional Anesthesia Techniques for Abdominal Operations

16

Tonia M. Young-Fadok and Ryan C. Craner

Introduction

Operations in the abdominal cavity are associated with a unique set of challenges. First and foremost they must deal with the underlying pathology and utilize whatever size incision is appropriate for that particular patient, whether open or minimally invasive. An additional challenge is the need to monitor and optimize gastrointestinal (GI) function after any operation on the abdominal cavity. Although the GI tract can develop ileus after any operation, particularly involving opiate medications or immobility, this is a particularly predominant feature after abdominal procedures.

In the past, regional anesthesia techniques for abdominal surgery were performed by anesthesiologists. This remains true of neuraxial techniques such as epidural and spinal analgesia, which are unique to that specialty. The availability of these techniques, however, varies depending on institutional expertise. With the advent of enhanced recovery after surgery (ERAS) and the emphasis on multimodality pain management, to improve patient care and to reduce opioid use, there has been a surge of interest among both anesthesiologists and surgeons in performing regional abdominal wall blocks, which can be divided into neuraxial and abdominal wall blocks.

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Basics: Dermatomes

It is important for the surgeon and anesthesiologist to be aware of the level of anesthesia needed for particular procedures, and an understanding of dermatomes is vital. A dermatome is the area of skin innervated by sensory fibers from a single spinal nerve. Important landmarks to remember are the fourth thoracic (T4) dermatome corresponds to the level of the nipples, the sixth thoracic (T6) dermatome the xiphoid, and the tenth thoracic (T10) dermatome the umbilicus (Fig. 16.1). To achieve surgical anesthesia for a given procedure, the extent of spinal anesthesia must reach a certain dermatomal level; for example, for upper abdominal surgery, the upper extent of analgesia must reach T4; for most abdominal procedures with incisions in the upper abdominal wall, it must reach T6; and in procedures where the incisions are all below the umbilicus, T10 is sufficient.

Neuraxial Anesthesia

Spinal Anesthesia

Spinal blocks may be used to avoid general anesthesia or in conjunction with it. Administration of local anesthetic (LA) with or without opioid in the subarachnoid space and into the cerebrospinal fluid (CSF) has long been used to provide surgical anesthesia while avoiding general anesthesia in operations where the incision is at or below the level of the umbilicus. This includes urological, gynecological, obstetric, and lower abdominal and perineal general surgery, in addition to lower limb vascular and orthopedic surgery. In the parturient pregnant patient, spinal anesthesia avoids potential complications associated with general anesthesia including the risks of airway management, intraoperative awareness, and aspiration events. A recent Cochrane review showed no evidence that regional anesthesia was superior to general anesthesia with regard to major maternal or neonatal

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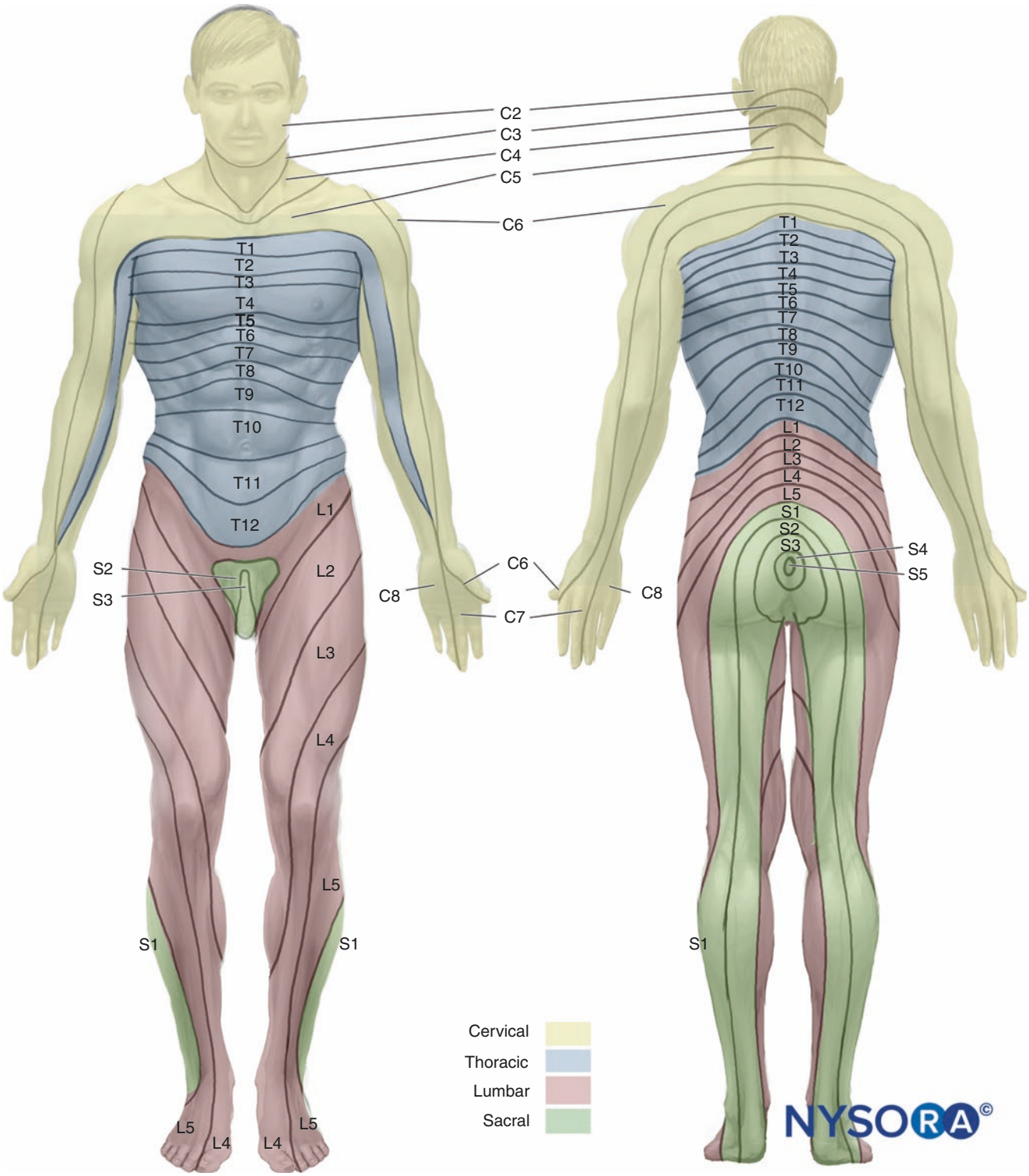

Fig. 16.1 Dermatomes. (© NYSORA. Reproduced by permission)

outcomes [1], spinal anesthesia remains preferred in obstetrics due to safety, reliability, and patient expectations.

Spinal anesthesia is also used in combination with general anesthesia to ameliorate the perceived risks of either approach alone. In patients undergoing upper abdominal procedures, spinal anesthesia may not prevent vagal reflexes and pain from traction on upper abdominal organs. Indeed, the motor and sensory block required to permit surgical manipulation of upper abdominal structures limits the safety of spinal anesthesia for those procedures. A spinal block

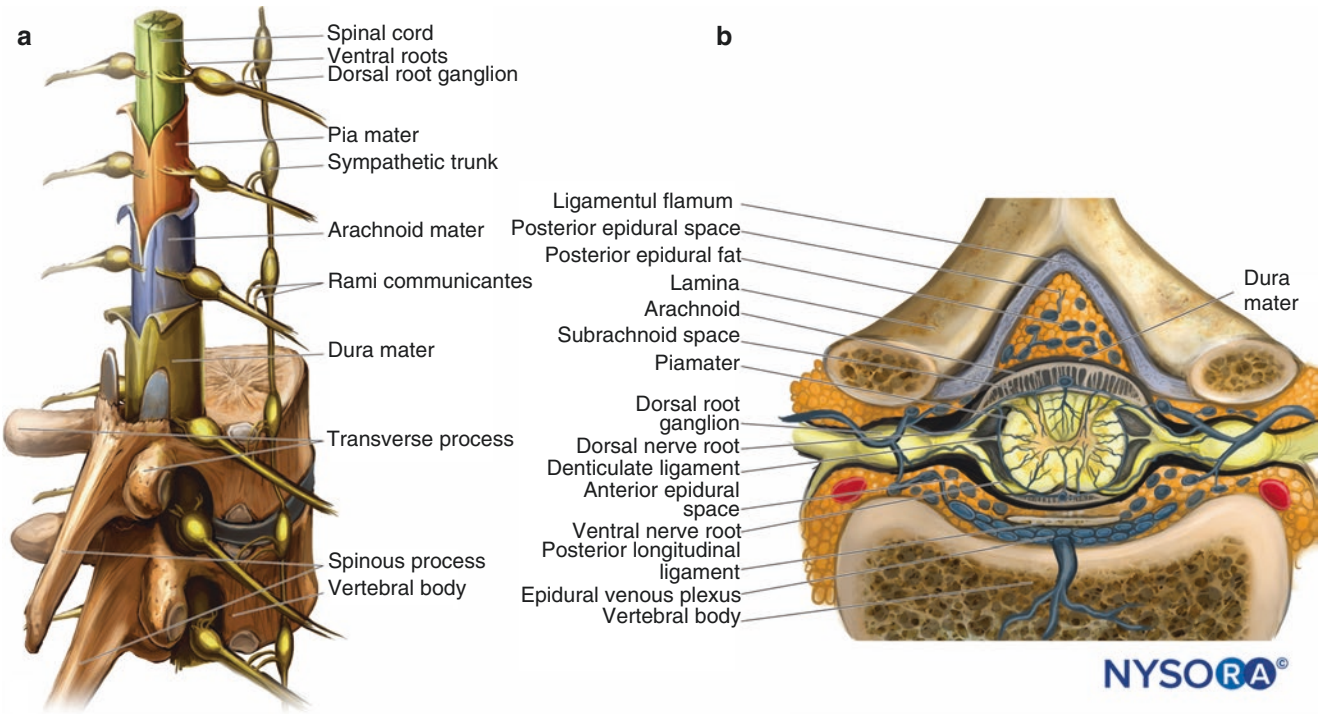

Fig. 16.2 Spinal and epidural anatomy. (© NYSORA. Reproduced by permission)

with dermatomal spread above the level of T-4-T6 dermatome results in intercostal and abdominal muscle weakness that may cause respiratory insufficiency as well as hypotension, bradycardia and possible asystole due to blocking of efferent sympathetic fibers [2]. However, spinal anesthesia in conjunction with general anesthesia has been used in surgery above the umbilicus, or in surgery where the incisions are below the umbilicus, but there is laparoscopic or manual manipulation of upper abdominal organs.

Anatomy

The vertebral column contains 33 vertebrae: 7 cervical, 12 thoracic, 5 lumbar, 5 fused sacral, and 4 fused coccygeal segments. Three membranes protect the spinal cord: the pia mater, arachnoid mater, and dura mater (Fig. 16.2). The subarachnoid space is the space between the pia mater and arachnoid, contains the CSF and spinal nerves, and is the target for spinal anesthesia. The subdural space lies between the arachnoid mater and dura mater and is the target for epidural blocks.

Equipment and Technique

The posterior midline approach is the commonest for placing a spinal [3]. The preferred position is to have the patient sitting, leaning forward to arch their lower back out. The decubitus position is an alternative but can introduce a lateral curve to the lumbar spine. The midline is identified by palpating the spinous processes and feeling for the soft area between the spinous processes to identify the interspace. The iliac crests are at the level of the L4 spinous process or the interspace between L4 and L5 vertebrae. An intercristal line can be drawn between the iliac crests to help locate this interspace. Either the L3–L4 interspace or the L4–L5 interspace is used to introduce the spinal needle. Because the spinal cord commonly ends at the L1–L2 level in 95–100% of patients, it is conventional not to attempt spinal anesthesia at or above the L3–L4 level.

In this position the needle traverses the skin, subcutaneous fat, supraspinous ligament, interspinous ligament, ligamentum flavum, dura mater, subdural space, arachnoid mater, and subarachnoid space.

The final choice of injectate is beyond the scope of this chapter, but there are basic principles to consider. The choice of local anesthetic is based on potency, onset, and duration of anesthesia and potential side effects. Potency is related to lipid solubility, duration is affected by protein binding, and onset is related to the amount of LA available in base form. The three most important adjustable factors determining spread of LA are baricity of the solution, position of the patient during and just after injection (gravity), and dose and volume of the anesthetic injected. Other variables include patient height, decreased cerebrospinal fluid (e.g., from increased intra-abdominal pressure due to pregnancy and obesity), site of injection, and needle bevel direction.

In addition, there are other medications that produce anesthesia and analgesia while limiting side effects. Local anesthetics and/or opioids +/− other adjuncts are used, including vasoconstrictors, opioids, α(alpha)2-adrenergic agonists, and acetylcholinesterase inhibitors, to enhance analgesia while reducing the motor blockade produced by LA.

Pros and Cons

Use of spinal anesthesia requires knowledge of indications and contraindications, plus an ability to weigh the risks and benefits of the procedure [3]. Absolute contraindications are patient refusal, infection at the site of injection, ongoing hypovolemia, allergy, and increased intracranial pressure. Relative contraindications include coagulopathy, previous spinal surgery, sepsis, fixed cardiac output, and indeterminate neurological disease. Major complications include direct needle trauma, infection with abscess or meningitis, vertebral canal hematoma, spinal cord ischemia, cauda equina syndrome, arachnoiditis, peripheral nerve injury, total spinal anesthesia, cardiovascular collapse, and death. Fortunately these are all extremely rare. Moderate complications include failed spinal and post-dural puncture headache. Minor complications are common and include nausea and vomiting, mild hypotension, shivering, itch, transient mild hearing impairment, and urinary retention.

Evidence

Within the context of early enhanced recovery protocols (ERP) and open surgery, epidural anesthesia rather than patient-controlled analgesia (PCA) was preferred to avoid systemic narcotics and their potential detrimental effects on bowel function [4]. With the more widespread use of laparoscopy, this notion was challenged. Levy at al. randomized 99 patients to receive epidural, spinal, or patient-controlled analgesia, in the setting of fluid-optimized patients in an enhanced recovery program [5]. The median length of hospital stay (LOS) was 3.7 days following epidural analgesia – significantly longer than that of 2.7 and 2.8 days for spinal analgesia and PCA, respectively ($p = 0{\cdot}002$ and $p < 0{\cdot}001$). There was also a slower return of bowel function with epidural analgesia than with spinal analgesia and PCA. Pain scores were higher in the PCA group in the early postoperative period. The authors concluded that spinal analgesia was the mode of choice, compared with epidurals or PCAs, but further studies including comparison with abdominal wall blocks were required to delineate the role in laparoscopic colorectal surgery within an ERP.

Another randomized controlled trial (RCT) compared spinal anesthesia vs. PCA, again within an enhanced recovery program [6]. Fifty patients were randomized either to a spinal mixture of bupivacaine and morphine or to a morphine PCA group. Postoperative opioid consumption in the spinal group was significantly less over the first three postoperative days ($p < 0.001$). There were no differences between the two groups in other outcomes (return of bowel function and dietary intake, readiness to hospital discharge, and LOS). The authors concluded that spinal anesthesia was associated with less opioid consumption but had no other advantages over systemic opioids.

Conversely, Koning et al. performed a RCT of 56 patients who received either single-shot intrathecal bupivacaine/morphine or a sham procedure, and both arms had access to PCA postoperatively [7]. Patients in the spinal group had shorter LOS (median 3 vs. 4 days, $p = 0.044$) and a significant decrease in opioid use and lower pain scores on the first postoperative day.

A retrospective analysis of 541 colorectal patients in an enhanced recovery program analyzed 7 protocol elements, including single-injection intrathecal hydromorphone-bupivacaine-clonidine immediately before general anesthesia [8]. Patients undergoing the spinal block had a median LOS of 3.2 days vs. 3.7 days vs. those who had contraindications to the block ($p = 0.008$). Use of less than 30 mg oral morphine equivalents (OME) in the first 48 hours was predictive of early discharge (odds ratio 2.0), and multivariable logistic regression showed that use of intrathecal analgesia was associated with OME <30 mg.

The original ERAS® guidelines [4] noted that a regional anesthetic block in addition to general anesthesia can minimize postoperative intravenous opiates, allowing rapid awakening, early enteral intake, and mobilization. The guidelines are often misquoted for recommending epidurals for pain management. The actual recommendation was that mid-thoracic epidural blocks using local anesthetics and low-dose opioids should be considered for open surgery, and in laparoscopic surgery, spinal analgesia or morphine PCA is an alternative to epidural anesthesia. In the more recent 2018 guidelines [9], the modified recommendation suggests avoiding opioids with multimodal analgesia including spinal/epidural analgesia or transversus abdominis plane (TAP) blocks when indicated.

In summary, while epidurals continue to have a role in open complex operations, they appear to be less beneficial in the case of laparoscopic surgery performed within enhanced recovery programs, where spinal analgesia can be considered if expertise is available.

Epidural Anesthesia

Epidural anesthesia is another type of neuraxial anesthesia that is based on anesthetizing the spinal nerve roots that traverse the subdural space, i.e., the potential space between the ligamentum flavum and dura mater. In the perioperative setting and in specific cases such as lower extremity, pelvic, or lower abdominal surgery, it can be used as the primary anesthetic. It is less often used in laparoscopic cases due to the

same limitations as noted previously for spinal anesthesia but can be a useful tool in addition to general anesthesia for many abdominal and thoracic operations. In addition, epidural analgesia can be an effective way to assist in management of postoperative surgical pain. Much of the discussion that follows is based on the intraoperative and postoperative use of an epidural catheter for pain management.

Anatomy

See section "Anatomy" under section "Neuraxial Anesthesia".

Equipment and Technique

In the perioperative setting, epidural anesthesia is commonly performed at the thoracic or lumbar vertebral levels. Unlike spinal anesthesia where analgesia is achieved at the level of injection and below, epidural anesthesia is limited to the dermatomal levels near the area of epidural insertion with the block density and cephalad and caudad spread being based on the volume and dosage of local anesthetic administered. For use of an epidural for postoperative pain management, a catheter is placed in the epidural space to allow for continuous infusion of local anesthetic with or without opioid.

After careful patient selection and informed consent, the patient is positioned in a manner that optimizes the chance of a straight path between the inferior and superior spinous process. This often involves flexion of the spine and may be done in the sitting or lateral decubitus position. Once the landmarks are identified by palpation or using ultrasound (US), the area is prepped using antiseptic solution including chlorhexidine or betadine. Spinal nerve irritation has been reported with exposure to chlorhexidine, so adequate time must pass for the solution to dry. Lidocaine is then infiltrated in the area of epidural insertion to anesthetize the skin and subcutaneous tissues. In a standard adult kit, a 17- or 18-gauge hollow needle is included; many commercial types are available. These needles have a curved tip to assist in advancement of a catheter once the needle is in position. Two anatomic approaches are utilized, either the midline or paramedian technique, with the latter being more often used in thoracic epidurals or in patients who are unable to flex the spine. The details of these approaches are beyond the scope of this text. For the midline approach, once the needle is engaged with the ligamentum flavum, a special loss-of-resistance (LOR) syringe filled with air or saline is attached. This syringe is often made of glass and allows a low resistance between the barrel and plunger of the syringe to allow a more tactile response as the ligamentum flavum is penetrated. The loss-of-resistance technique is completed with gentle advancement of the needle/syringe together while depressing the plunger awaiting the loss of resistance where the air or saline is injected freely, presumably into the epidural space. Once this occurs the epidural catheter included in the kit is advanced and ultimately positioned with 4–6 cm of catheter in the epidural space. A test dose of 3 mls of local anesthetic with epinephrine (usually 1.5% lidocaine with 1:200,000 epinephrine) is injected to assess for inadvertent intrathecal (progressive weakness below level of injection including legs/feet) or intravascular (tachycardia/hypertension from epinephrine effect) placement.

Pros and Cons

In open surgery the benefits of epidural analgesia include improved pain scores at rest and with movement and reduced requirement of other analgesics. It has also been shown to reduce pulmonary complications, reduce rates of ileus, and decrease the surgical stress response [10]. These benefits are not reliably seen in laparoscopic surgery.

The risks of epidural analgesia include block failure, hypotension, motor weakness, urinary retention, or epidural hematoma. The 3rd National Audit Project (NAP3) study reports that epidurals can cause permanent injury or death in somewhere between 1 in 5800 and 1 in 12,200 cases [11]. To avoid or reduce the risk of complications, careful patient selection must be employed including perioperative anticoagulation management, fastidious insertion technique, and proper postoperative management.

Evidence

The impact of epidurals on metabolism has been mainly shown for open surgery. Epidural blockade with local anesthetics – before, during, and after surgery – reduces neuroendocrine and catabolic responses to surgery [12], such as attenuation of insulin resistance [13], and minimizes protein breakdown [14]. Epidural anesthesia has also been associated with reduction in proinflammatory cytokines and inflammatory markers after major abdominal surgery [15, 16].

The gold standard in open colorectal surgery is thoracic epidural analgesia (TEA) (T7–T10). Several RCTs and meta-analyses have shown improved pain control compared with systemic opioids [17, 18]. Although widely performed, lumbar epidural blockade is less effective, with insufficient upper abdominal sensory block and increased lower extremity motor block and urinary retention [12]. TEA may also improve postoperative outcomes in open surgery. A multicenter RCT assessing TEA plus general anesthesia on 30-day morbidity or mortality in high-risk patients after major open gastrointestinal surgery did not show any benefit [19]. However, subsequent meta-analyses have shown that TEA results in earlier recovery of bowel function after colorectal surgery [20–22] and reduces respiratory [22, 23] and cardiovascular complications [22]. There is, however, a higher risk of postoperative arterial hypotension and urinary retention [22].

The analgesic benefits are not seen in patients undergoing laparoscopic colorectal surgery [24] where epidurals may increase LOS. A meta-analysis including five RCTs of patients undergoing laparoscopic colorectal surgery treated with an ERAS protocol did not demonstrate the same benefits [25]. TEA has no impact [26] or even delays [24, 25, 27]

hospital discharge in patients undergoing laparoscopic colorectal surgery, possibly due to a higher incidence of hypotension, urinary retention, or motor blockade [24, 28]. TEA might still be valuable in patients with chronic pain, opioid-dependent patients, or patients with a high risk of conversion to an open operation.

An epidural infusion mixture of local anesthetic and lipophilic opioids provides better analgesia than either alone [17, 18, 29]. TEA is best if initiated before surgery and continued in the intraoperative and postoperative period, for 48–72 hours [30] to reduce systemic opioids. One major disadvantage is high epidural failure rates of 22–32%. Use of epidurals also requires a postoperative pain team.

There are several reports of association between epidural anesthesia and improved survival after cancer surgery [31, 32], but results for this outcome are mixed [33]. The oncologic impact of epidurals on colorectal cancer recurrence and metastasis [34, 35] requires further investigation, especially in the context of an ERAS program.

Abdominal Wall Blocks

Paravertebral

Paravertebral blocks are mentioned for the sake of completeness. Thoracic paravertebral blocks (TPVB) have been used for unilateral anesthesia and analgesia for thoracic and some thoracolumbar procedures, such as thoracotomy, thoracoabdominal esophageal surgery, cholecystectomy, and renal surgery. However, the technique has only gained traction in general surgery for unilateral breast surgery and herniorrhaphy. This results from the unilateral and highly dermatome-dependent nature of the technique, which involves injecting local anesthetic alongside the thoracic vertebra close to where the spinal nerves emerge from the intervertebral foramen. The injectate has variable spread, and potentially requires multiple levels of infiltration, especially if larger dermatomal areas are to be anesthetized. For the thoracic dermatomes, the path of approach of the injectate needle needs to be inserted at the level of the chosen vertebral process and then "walked off" the transverse process of the vertebra above, all while making sure that the depth of the needle's approach is monitored in order to avoid pneumothorax [36]. Ultrasound assisted or ultrasound guided paravertebral block has improved the safety and efficacy of the paravertebral block [37]. A recent single institution review of ultrasound guided TPVB for breast surgery reviewed 1427 injections with complications occurring in six patients including bradycardia and hypotension (n = 3), vasovagal episode (n = 1) and possible local anesthetic toxicity (n = 2). There was no incidence of accidental pleural puncture or symptomatic pneumothorax [38]. The arguments against this approach for an abdominal operation include the risk of inadvertent pleural puncture, which although rare, still can occur if the needle is not visualized throughout the procedure. This is in addition to discomfort during the procedure as the local anesthetic is administered. Also, depending on the area of the surgical field and laterality, multiple bilateral injections may be required.

Quadratus Lumborum

Quadratus lumborum (QL) blocks belong to a group of four blocks that are defined by where the injectate is deposited relative to the anatomy of the QL muscle. These blocks have been classified as QL 1 (lateral), QL 2 (posterior), QL 3 (anterior or transmuscular QL also known as TQL or tequila block!), and QL IM (intramuscular).

Anatomy

The quadratus lumborum muscle is a quadrilateral-shaped muscle of the posterior abdominal wall. Its origin is along the posterior aspect of the iliac crest, and it inserts superiorly onto the 12th rib and medially onto the transverse processes of L1–L4 vertebrae. The QL muscle is between the anterior and middle layers of the thoracolumbar fascia (Fig. 16.3). The psoas muscle is anterior to the QL muscle, and the erector spinae muscle is posterior.

Equipment and Technique

The lateral decubitus position provides the best access and visualization of the neuraxial structures. A low frequency (5- to 2-MHz) curved array ultrasound transducer, commonly used in the operating room for central line placement, can be used. A 22-gauge needle is used, although some sources advise a peripheral nerve stimulator to prevent needle advancement if the needle is too deep and is adjacent to the lumbar plexus.

For the anterior/transmuscular QL, the transducer is placed on the patient's flank just cephalad to the iliac crest. The "shamrock sign" is identified, whereby the transverse process of the L4 vertebra is the stem, and the three leaves of the trefoil are the erector spinae posteriorly, QL laterally, and psoas major anteriorly. The needle is advanced through the QL muscle, and the injection target is the fascial plane between the QL and psoas major muscles (Fig. 16.3).

For the lateral or QL 1 block, the transducer is placed in the midaxillary line and moved posteriorly until the transversus abdominis aponeurosis is seen. The needle is aimed deep to this aponeurosis, and the injectate is deposited between the aponeurosis and superficial to the transversalis fascia at the lateral border of the QL muscle (Fig. 16.3). Spread in this plane involves the lateral cutaneous branches of the iliohypogastric, ilioinguinal, and subcostal nerves (T12–L1).

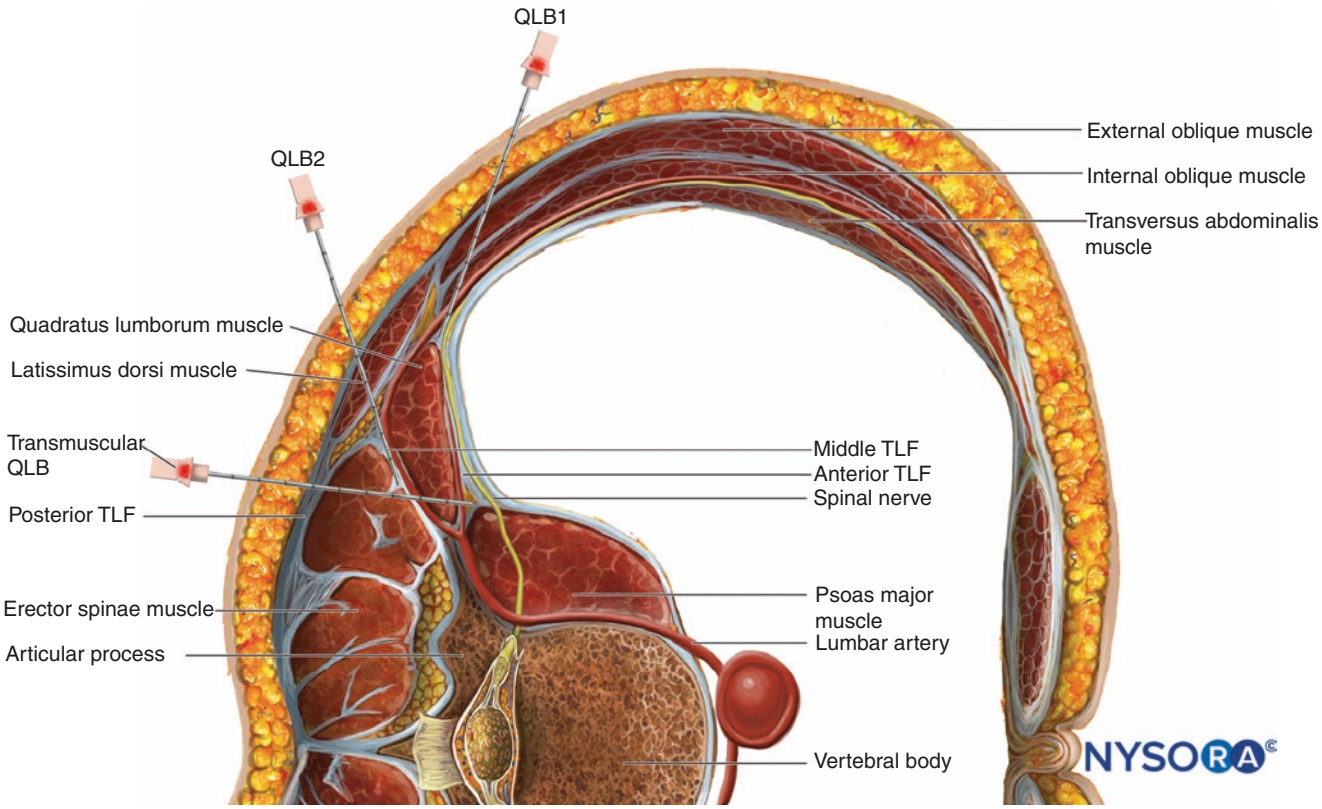

Fig. 16.3 Quadratus lumborum blocks (QLB). TLF thoracolumbar fascia. (© NYSORA. Reproduced by permission)

In the posterior or QL 2 block, the transducer is placed in the midaxillary line and moved posteriorly until the lateral interfascial triangle (LIFT), which encapsulates the paraspinal muscles, is reached. The middle layer of the thoracolumbar fascia (TLF) separates the QL and erector spinae muscles. The tip of the needle is advanced until it is inside the middle layer of the TLF near the LIFT (Fig. 16.3). The extent of analgesia is similar to the anterior or TQL block, but the onset is more rapid.

Pros and Cons

The QL 1 or lateral QL block reliably covers T10–L1 and is likely similar to the "posterior" TAP block. Both the posterior/QL 2 and the anterior/QL 3/transmuscular QL blocks cover the dermatomes from T4 to T12/L1 and affect the anterior and lateral cutaneous branches of the nerves. Hence these two blocks are preferable for abdominal procedures where the incision(s) extend above and below the umbilicus. QL blocks may provide visceral analgesia due to their paravertebral and possibly epidural spread.

There are several potential drawbacks to these blocks. QL 1 and QL 2 blocks are considered to require intermediate ultrasound and proprioceptive skills, whereas QL 3 requires advanced skills. The requirement for ultrasound and the need to change the lateral decubitus position of the patient to perform bilateral blocks increase procedure time. There is also the potential for injury to the kidney or lumbar vessels. Lower extremity weakness occurs in just 1% of lateral/QL1 blocks, in 19% of posterior/QL2 blocks, and in up to 90% of anterior/QL3 blocks.

Evidence

Carline et al., in a cadaver dye study, showed that anterior/transmuscular/QL 3 blocks more consistently blocked lumbar nerve roots than lateral/QL1 and posterior/QL2 blocks [39]. In another cadaver dye study, Adhikary et al. showed dye staining of the upper lumbar plexus in 70% of specimens [40].

These anatomic studies correlate with the findings of a large retrospective study of 2382 patients, performed by Ueshima et al. [41] The rates of quadriceps muscle weakness varied dramatically depending on the type of block: 1% in lateral QL, 19% in the posterior QL, 90% in anterior/transmuscular QL, and 0% in intramuscular QL.

There are no randomized controlled trials comparing one type of QL block with another. There are RCTs comparing QL blocks with either sham blocks or TAP blocks.

Blanco et al. randomized 50 patients following Cesarean section to a QL block (in this case QL 2/posterior) with 0.125% bupivacaine versus the same QL block performed with normal saline. The study patients used less morphine and had lower visual analogue scale (VAS) scores at 6 and 12 hours

but not at 24 hours [42]. This group reported the initial ultrasound-guided QL block in 2007, which described deposition of local anesthetic adjacent to the anterolateral aspect of the QL muscle. They showed that local anesthetic spread occurred into the thoracic paravertebral space, similar to spread after the original tap block, which described injection in the triangle of Petit [43]. However, the injectate was noted to spread anteriorly in the TAP plane after midaxillary and anterior subcostal approaches to TAP blocks. The difference in local anesthetic spread likely explains the improved extent and duration of analgesia after a QL block compared with TAP block.

These authors performed additional magnetic resonance imaging (MRI) studies using two different blocks: the original anterolateral one and a second one, QLB2, posterior to the muscle [42]. MRI showed that the injection posterior to the QL muscle, between the QL and latissimus dorsi muscles, resulted in more predictable spread of injectate into the paravertebral space. This also had better ultrasound images, was easier to perform because of a more superficial injection site, and was potentially safer because the needle tip was separated from the peritoneum, reducing the risk of bowel injury. The authors subsequently abandoned the anterolateral approach to use the posterior block.

Krohg et al. randomized 40 elective C-section patients to either lateral QL block or sham injection with saline and found reduced opioid consumption and low analgesics scores in the treatment arm [44].

In an RCT of 76 elective C-section patients randomized to posterior QL versus TAP, the treatment arm used significantly less morphine at 12, 24, and 48 hours after delivery [45]. Another RCT of posterior QL versus TAP randomized 53 children undergoing unilateral inguinal hernia repair or orchiopexy surgery. In the QL group, the number of patients requiring analgesia in the first 24 hours was significantly lower [46].

In summary, the posterior QL/QL 2 block produces better extent of abdominal analgesic coverage than the lateral/QL 1 block and is technically less difficult, safer, and produces a far lower rate of lower extremity weakness than the anterior/transmuscular/QL 3 block.

Transversus Abdominis Plane

Transversus abdominis plane, or TAP, blocks have become widely adopted. Unfortunately they have also become widely adapted, and in the process, certain versions have become a less effective rendition of the original block.

Anatomy and History of Use (and Misuse)

The anterolateral abdominal wall contains three muscles and their fascial coverings (Fig. 16.4a, b). From external to internal, these are the external oblique (EO), internal oblique (IO), and transversus abdominis (TA) muscles. The correct TA plane is the plane superficial to/on top of/external to the transversus abdominis muscle and below the fascia beneath the IO muscle (Fig. 16.5). On the surface of the TA muscle, and adherent to it, the intercostal, subcostal, and L1 segmen-

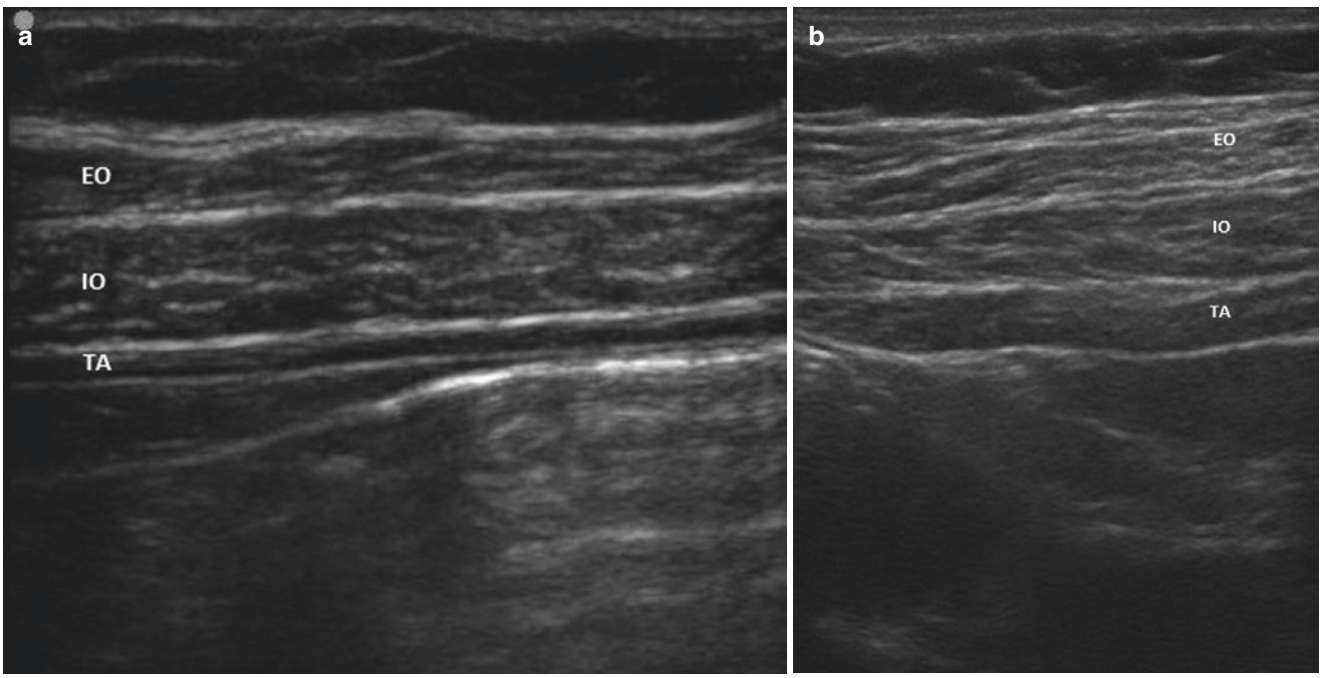

Fig. 16.4 (**a**) Abdominal wall muscles. (**b**) Anterolateral abdominal wall muscles. EO external oblique, IO internal oblique, TA transversus abdominis

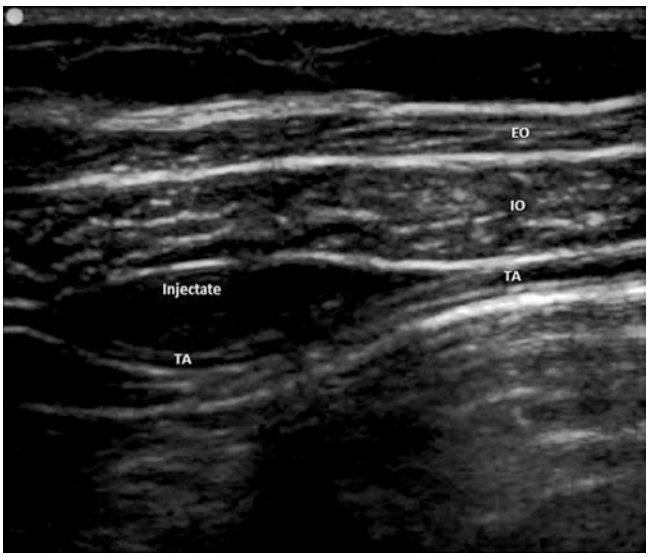

Fig. 16.5 Injection in transversus abdominis plane (TAP). EO external oblique, IO internal oblique, TA transversus abdominis

tal nerves communicate to form the upper and lower TAP plexuses, which innervate the anterolateral abdominal wall [47]. Since nerves originating from the T6 to L1 spinal roots run in this plane and supply sensory nerves to the anterolateral abdominal wall, local anesthetic spread in this plane theoretically provides analgesia to the anterolateral abdominal wall. A *complete* blockade of the TA plane requires anesthesia of *both* the upper plexus (T6–T9), with a subcostal or rectus block, *and* the more widely performed block of the lower TAP plexus (T10–L1).

It is helpful to be aware of the history of TAP blocks, how the block is being performed, and who is doing it, to understand the rather disparate versions of TAP blocks that have been disseminated and popularized:

- *Classic TAP – Posterior* – The earliest report of a TAP block was by Rafi who described a landmark-defined approach via the Triangle of Petit; this is now referred to as a posterior approach [43]. A "2-pop" technique was described, with the pops attributable to traversing the aponeuroses of the EO and IO muscles.
- *Ultrasound TAP – Lateral* – With the interest generated by ERAS, the opioid epidemic, and multimodality analgesia, in addition to more widely available compact mobile ultrasound devices in the OR, TAP blocks became technically easier and safer to perform, initially by anesthesiologists. The classic block used landmarks that are absent in about 17% of patients – and obscured by adiposity in many of the remainder! Hence anesthesiologists used ultrasound to confirm the correct plane and to avoid entering the peritoneal cavity. The use of US allowed a midaxillary block between the costal margin and iliac crest, where three layers of fascia must be traversed to reach the correct plane on the surface of the TA muscle, but with US the "2-pop" technique was not necessary, as the correct plane could be visualized. Also the block could be performed with the patient supine, i.e., the position used for the operation. This lateral TAP block, between the IO and TA muscles, should reach intercostal nerves T10–T11 and the subcostal nerve T12. The L1 segmental nerves in the TAP are not covered by the lateral TAP block and require an anterior TAP block medial to the anterior superior iliac spine.
- *Lap TAP – Anterior* – Surgeons became aware of TAP blocks and the "2-pop" technique and realized that in laparoscopic cases (and also open), the most feared complication of TAP blocks (i.e., injury of abdominal organs) could be avoided as the tip of the needle is seen if it passes too far through the abdominal wall. Thus the "Lap TAP" was developed. Two adjustments in technique, however, rendered the block less effective: relying on "2 pops" meant the tip of the needle is now in the IO muscle above the fascia rather than on top of the TA muscle, and the constraints of the drapes mean that the block is generally given in the anterior axillary line rather than the midaxillary line.
- *Subcostal Block* – The limitation of the aforementioned TAP blocks is that the upper level of analgesia is T10, the umbilicus, so upper abdominal incisions are not covered. The subcostal approach to the TA plane addresses the intercostal nerves T6–T9 between the posterolateral rectus abdominis sheath and the anteromedial extent of the transversus abdominis muscle.
- *Rectus Muscle Block* – This is also an attempt to produce analgesia of the T6–T9 nerves, but within the rectus sheath, after the nerves have exited the TA plane and course between the upper rectus muscle and the posterior rectus sheath. This can be performed with US or as a semi-blind, laparoscopic visualized approach.

Equipment and Technique

- *Classic TAP – The classic T*AP block, introduced by Rafi in 2001, was a *landmark-guided technique* via the Triangle of Petit, or lumbar triangle, to achieve a field block [43]. It described the injection of local anesthetic in the plane between the IO aponeurosis and TA muscle within the borders of the triangle of Petit, a specific region in the lateral abdominal wall in the midaxillary line, where the base of the triangle is formed by the iliac crest, the anterior margin is the edge of the external oblique muscle, and the posterior margin is the latissimus dorsi. In this triangle, in order to reach the surface of the TA where the nerves interweave, an external needle is passed

through the skin and subcutaneous tissue, and then "2 pops" are felt as the two aponeuroses of the external oblique (EO) and internal oblique (IO) muscles are traversed. This is a blind technique.

- *US TAP* – Typically a mobile compact US unit and a 22-gauge needle, spinal needle, or nerve stimulator needle are used. The TAP is accessed in the midaxillary line, between the costal margin and iliac crest, and a 2–5 ml bolus of saline is used first to confirm correct placement prior to injection of local anesthetic (Fig. 16.5). The "2-pop" technique is not necessary as the plane is confirmed by US.
- *Lap TAP* – With increased use by anesthesiologists, there was a concomitant surge of interest among surgeons using the "2-pop" technique intraoperatively. Unfortunately, the technique was popularized without awareness of an important detail: The "2-pop" technique is only applicable in the Triangle of Petit. Surgeons tend to perform the technique in the anterior axillary line, limited by the surgical drapes, and so *three* fascial layers need to be traversed to reach the surface of the TA muscle.

  Although this author no longer supports the use of the blind Lap TAP because of the potential misunderstanding of the original technique described above, the following technique has been widely disseminated. With the patient prepped and draped for an abdominal operation, a point halfway between the costal margin and iliac crest/anterior superior iliac spine is identified in the anterior axillary line. A 22G needle is "blunted" by tapping it against a hard surface. This forms a slight burr at the tip of the needle and introduces the sensation of resistance as it passes through fascia. The needle is then advanced through the skin (a major "pop" but not one of the two counted) and then experiences two further pops. Based on the 2-pop technique, this is when the local anesthetic is injected. As seen in the diagram of the three abdominal wall muscles, this technique when performed outside of the Triangle of Petit traverses the fascia superficial to the EO and then the fascia external to the IO, leaving the tip of the needle in the IO muscle, and not on the surface of the TA muscle. This likely explains the high rate (up to 35%) of deposition of dye in the IO in studies of the blind technique [48] but not why patients also seem to gain some benefit from this approach. One may surmise that there is local anesthetic effect across the fascia on the surface of the TA muscle.
- *Subcostal/Upper TAP* – The upper anterior part of the TA muscle lies posterior to the lateral edge of the upper rectus abdominis muscle and can be visualized by US beneath the costal margin (Fig. 16.6). A linear US transducer is placed beneath the costal margin to identify the rectus muscle and then is moved laterally to visualize where the lateral edge of the muscle and posterior rectus sheath overlap the transversus abdominis muscle. The target is the spread of local anesthetic between the posterior rectus sheath and the anterior margin of the transversus abdominis muscle. This approach anesthetizes the intercostal nerves T6–T9.
- *Rectus Block* – A simple version of blocking the upper abdominal wall nerves is to encounter them after they transition from the surface of the TA muscle to the posterior aspect of the upper rectus muscle, anterior to the posterior rectus sheath. This approximates the effect of the subcostal block. Under US visualization, the needle is advanced to the posterior aspect of the rectus muscle, anterior to the rectus sheath (Fig. 16.7). In the blind/laparoscopic visualized approach, after the skin there is one "pop" through the anterior rectus fascia before traversing the muscle and meeting some resistance from the posterior fascia, which should not be traversed. As the depth of the rectus muscle is highly variable, this approach is best performed under US guidance for accurate injection.

Pros and Cons

Potential injuries are related to completely blind TAP blocks, where the tip of the needle traverses the abdominal wall beyond the parietal peritoneum and can theoretically injure bowel. This is unlikely when performed with US by an experienced clinician. Under laparoscopic visualization, it can be determined when the tip of the needle has passed beyond the innermost fascia and entered the preperitoneal area or the peritoneal cavity and can be adjusted. The needle can be withdrawn slightly, but it remains an educated guess whether the tip is on the surface of the TA muscle unless this is observed by US. One study, using dye injectate followed by dissection, indicated that the blind technique results in deposition in the correct plane in only 23% of cases. The most common incorrect plane is within the IO muscle [48] – likely a result of the "2-pop" technique without understanding of the three fascial entities that need to be traversed when outside the Triangle of Petit.

The nature of the injectate determines when the block should be performed – at the beginning versus the end of the case. Shorter-acting local anesthetics, of 2–8 hours duration, may be best deployed at the end of the case. If an institution has access to liposomal local anesthetic preparations, which can last up to 72 hours, this is likely best injected at the beginning of the case to minimize intraoperative opioid use.

Evidence

A systematic review and meta-analysis of 51 RCTs of TAP blocks evaluated the role of TAP vs. various control groups [49]. TAP block vs. placebo reduced pain scores and mor-

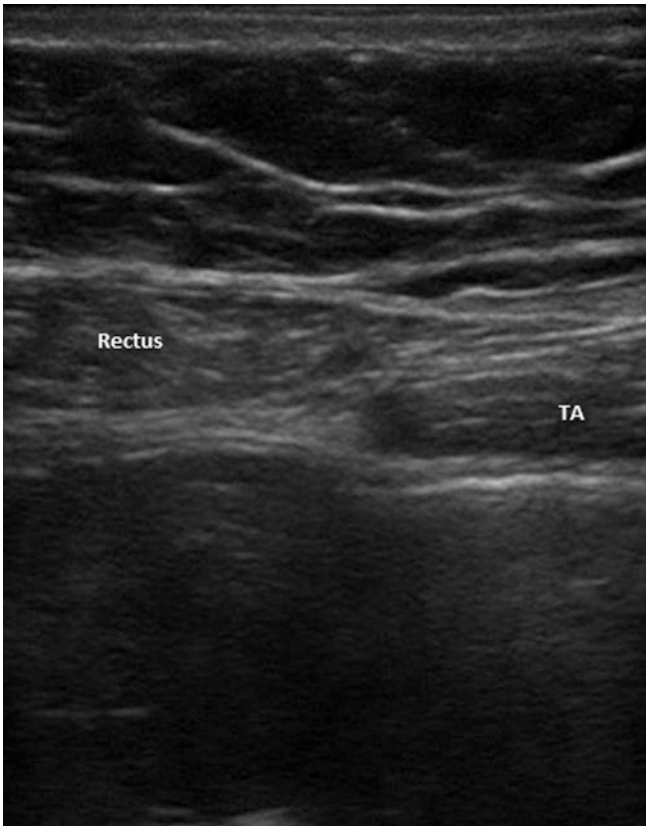

Fig. 16.6 Rectus subcostal muscles. TA transversus abdominis

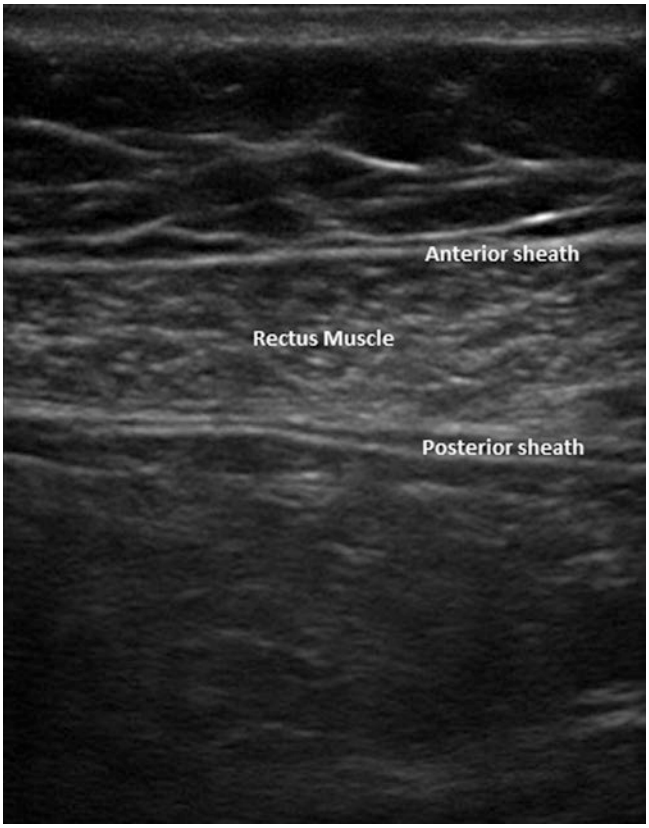

Fig. 16.7 Rectus muscle

phine consumption after gynecological surgery, appendectomy, inguinal surgery, bariatric surgery, and urological surgery. When compared with intrathecal morphine, however, TAP blocks had less analgesic efficacy.

There are two Cochrane systematic reviews of TAP blocks. Hamilton et al. identified trials of liposomal bupivacaine peripheral nerve block for the management of postoperative pain up to January 2016 that were randomized, double-blind, placebo- or active-controlled clinical trials of a single dose of liposomal bupivacaine administered as a peripheral nerve block in adults undergoing elective surgery at any surgical site [50]. There were insufficient data to perform a meta-analysis. Of four published studies, only two investigated liposomal bupivacaine TAP block. The authors concluded there is a lack of data to support or refute the use of liposomal bupivacaine administered as a peripheral nerve block for the management of postoperative pain.

An earlier inconclusive Cochrane review included RCTs of abdominal surgery comparing TAP or rectus sheath block with no TAP or rectus sheath block; placebo; and systemic, epidural, or any other analgesia [51]. They found five studies assessing TAP blocks: three used US guidance, and two used loss-of-resistance/landmark methods. There was limited evidence that TAP block reduces opioid consumption and pain scores after abdominal surgery when compared with no intervention or placebo.

Since the most recent Cochrane review in 2016, a search for RCTs with full text in Core Clinical journals produced five studies: three in Cesarean delivery/hysterectomy, one for donor nephrectomy, and the other in laparoscopic colectomy. The latter was a small study randomizing 27 patients in each arm undergoing bilateral TAP block plus rectus sheath block, comparing a control group receiving levobupivacaine in saline versus a study group receiving levobupivacaine in low-molecular weight dextran [52]. The intervention arm decreased the risk of levobupivacaine toxicity while providing better analgesia. This study highlights the use of adjuvants in addition to local anesthetics, to improve the spread and duration of blocks and minimize potential side effects.

An additional search of evidence for TAP blocks produced 325 results, of which 123 were listed as randomized controlled trials. The studies vary widely, including different techniques (blind vs. US guided), injectate composition and volumes, comparison groups (wound infiltration, spinal, placebo, etc.), and procedures ranging from Cesarean delivery, through colorectal surgery to ovariectomy in cats! The underwhelming quality of the studies in the two Cochrane trials and lack of consensus regarding approach belie the zeal

with which many surgeons and anesthesiologists perform these blocks. There is considerable room for research to optimize this approach.

Transversalis Fascia

A blind Lap TAP in the anterior axillary line is easy, safe, and quick to perform by surgeons. An US-guided TAP block, performed more posteriorly in the midaxillary line with visualization of the correct plane, appears to be more effective but takes longer and requires US experience. A quadratus lumborum block is effective, is posterior, is closer to the origin of the nerve roots, but also requires US, and the anatomy is more complex. In the quest to develop a simple, safe, effective block, the fascial planes between the US TAP and the lateral QL blocks have been re-evaluated.

Anatomy

The fascia on the peritoneal cavity side of the TA muscle is the transversalis fascia (Fig. 16.8). This continues its course posteromedially and becomes continuous with the fascial planes around the QL muscle. This fascia can easily be accessed more posteriorly than an US TAP, by the surgeon operating in the abdominal cavity (either laparoscopically or open), as far posteriorly as the lateral peritoneal reflections, i.e., where the retroperitoneal fat covering the kidneys and psoas muscles extends to the posterolateral abdominal side wall (Fig. 16.9).

Equipment and Technique

A laparoscopic decompression needle with a beveled tip is attached at its hub to connector tubing and then to a 20 ml injection syringe. The tubing prevents movement of the tip as the syringe is exchanged. Under direct visualization, the transversalis fascia (TF) is identified just caudad to the costal margin (i.e., more cephalad than the usual TAP block), right before it becomes hidden under retroperitoneal fat at the lateral peritoneal reflection of the colon. Using a lower quadrant port on that side, the needle is aligned slightly obliquely to the fascia with the bevel facing medially and advanced under the fascia. This can often be felt as a slight "click." As the injectate is delivered, there should be no bleb in the parietal peritoneum, but a slight swelling of the TF may be noticed.

Pros and Cons

The procedure is as quick and simple as a Lap TAP, but the plane is more accurately accessed (see below) as the bevel of the needle approximates the course of the fascia rather than being perpendicular to it. No US experience is required, and the tip of the needle is visualized until it passes beneath the fascia, so there is no risk of injury to intra-abdominal organs. There has been no evidence of leg weakness with this technique, unlike some of the QL block approaches.

Evidence

Data from sequential PDSA (Plan, Do, Study, Act) cycles, as part of a quality improvement project, were presented at a national peer-reviewed meeting [53]. The TF block reduced opioid consumption by 70% compared with the Lap TAP block, and PCA devices were eliminated for elective surgery. Cadaver studies comparing this TF block with US TAP show improved spread of injectate both posteriorly and also in the cephalad/caudad directions.

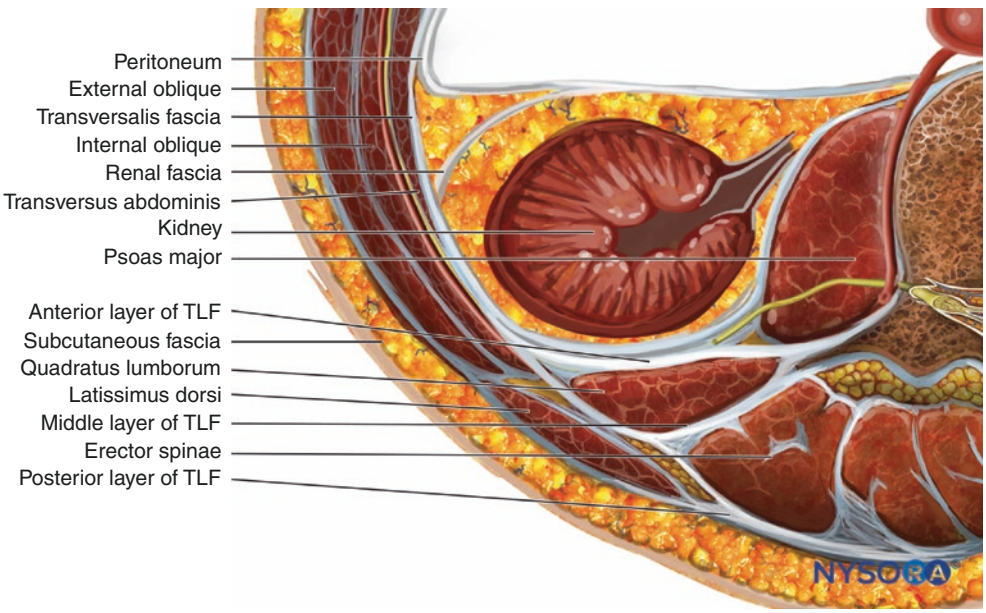

Fig. 16.8 Transversalis fascia anatomy. TLF thoracolumbar fascia. (© NYSORA. Reproduced by permission)

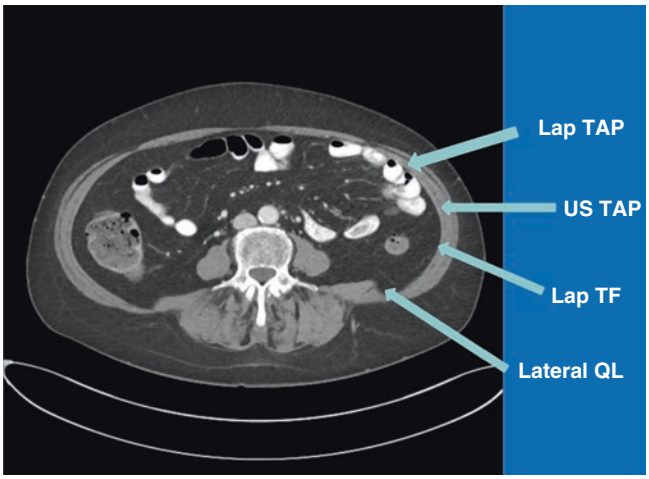

Fig. 16.9 Fascial planes for blocks: Lap TAP, US TAP, LAP TF, lateral QL. Lap laparoscopic, TAP transversus abdominis plane, US ultrasound, TF transversalis fascia, QL quadratus lumborum

Conclusion

Regional anesthesia techniques now allow combinations of techniques beyond general anesthesia versus neuraxial anesthesia, i.e., either spinal or epidural. The pressure to minimize or even completely avoid opioids postoperatively and preferably also intraoperatively has led to investigation of alternative abdominal wall analgesia techniques. This requires an emphasis not just on pain management intraoperatively, to allow an operation to be performed, but forethought regarding pain management postoperatively, which is an opportunity to use different modalities in conjunction, obviating the need for opioids and optimizing the patient's recovery.

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Prevention of Intraoperative Hypothermia

17

William J. Fawcett

Introduction

The maintenance of normothermia is a key physiological process, and while there are normal cyclical temperature variations that occur in relation to menstrual and circadian cycles as well as in the ageing process [1, 2], many of the enzymatic processes and other cellular functions have a narrow range of temperature for optimal function. Under normal circumstances, a finely tuned system of temperature sensation, central integration, and effector mechanisms are in place to preserve temperature homeostasis, but patients undergoing surgery, either under general anesthesia or regional anesthesia (and particularly both), are prone to hypothermia, with a number of adverse sequelae. Temperature loss and inadvertent hypothermia (IPH) are an ever-present risk for patients undergoing anything more than the most minor surgery, and it is essential that steps are taken to accurately measure temperature, prevent hypothermia, and restore normal core body temperatures.

The prevention of IPH, defined as a temperature of <36 °C, is a fundamental standard of care for all patients undergoing surgery [3] as normal body temperature is crucial to optimize critically temperature-dependent cellular activities [2]. Patients who experience IPH have the potential for a number of adverse outcomes, as shown in Table 17.1 [2–5].

IPH is common, even when forced air warmers (vide infra) are employed, affecting about two-thirds of patients 45 minutes after induction (<36.0 °C), with nearly a third of patients reaching a core temperature <35.5 °C, although temperatures did rise thereafter, reaching an average final temperature of 36.3 °C [3]. The impact of preventing hypothermia for the shorter procedures and its impact on outcome is largely unknown [6]. IPH needs to be distinguished from induced hypothermia (or targeted temperature management), which has been variously described for cardiac, neurosurgery, out-of-hospital cardiac arrests, neonatal ischemic encephalopathy, and head injures [5]. The aim of this chapter is to provide a wide cover on this topic with particular relevance to enhance the understanding on how patients can lose heat during surgery and the pathophysiology of its impact as well as recommendations to avoid hypothermia.

Why Patients Lose Heat

The usual thermoregulatory processes to control core body temperature are finely tuned to within a few tenths of a degree. The process whereby this occurs is a classic example of a physiological negative homeostatic feedback mechanism [1]. Afferent sensors in the skin and central nervous system (particularly the family of transient receptor potential [TRP] protein ion channels) input to a central regulator (principally the hypothalamus but other areas of the central nervous system too including the spinal cord), and then effectors mechanisms restore deviations in temperature to normal via behavioral and autonomic responses (such as shivering arteriovenous vasoconstriction) [2]. A key area of this process is that the threshold activations for sensors,

Table 17.1 Consequences of hypothermia [2–5]

Consequences of hypothermia
Coagulopathy (especially reduced platelet function)
Increased blood loss and increased blood transfusion requirements
Increase in surgical site infections (SSIs)
Delayed drug biotransformation
Prolonged recovery from anesthesia
Increased in myocardial complications related arrhythmias, increased systemic vascular resistance, and myocardial workload
Magnified stress response
Reduced blood flow to viscera (liver and kidney)
Increased hospital length of stay
Patient discomfort
Shivering with increased oxygen requirements

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effectors, and central regulation work within very narrow margins. In addition, brown fat in neonates and infants provides non-shivering thermogenesis, whereby oxidative metabolism is uncoupled from adenosine triphosphate (ATP) production, and energy is expended in the form of heat; but this process is of thought to be of minor relevance in adults [1, 2].

Both general and neuraxial anesthesia impair these finely tuned processes. For general anesthetics there is a dose-dependent reduction for both shivering and vasoconstriction, such that the latter is not activated until 34 °C or lower. This is the major effect, rather than impairment of vasoconstriction or shivering. Neuraxial anesthesia also has marked effects on thermoregulatory control mechanisms at various points of the pathway from reduced neural input, reduced central (hypothalamic) threshold activation, and inhibition of neurally mediated effector responses (shivering and vasoconstriction), with greater dermatomal block heights producing correspondingly more thermoregulatory impairment than lesser degrees of block [7].

The effects of general anesthesia and neuraxial anesthesia are generally considered to have an additive effect [8]. In addition to the above, volitional behavioral responses triggered by changes in temperature have a very important effect on thermoregulatory control in humans and are clearly not available to surgical patients. Patients undergoing surgery under sedation alone or with peripheral nerve blocks are usually able to maintain their body temperature unaided.

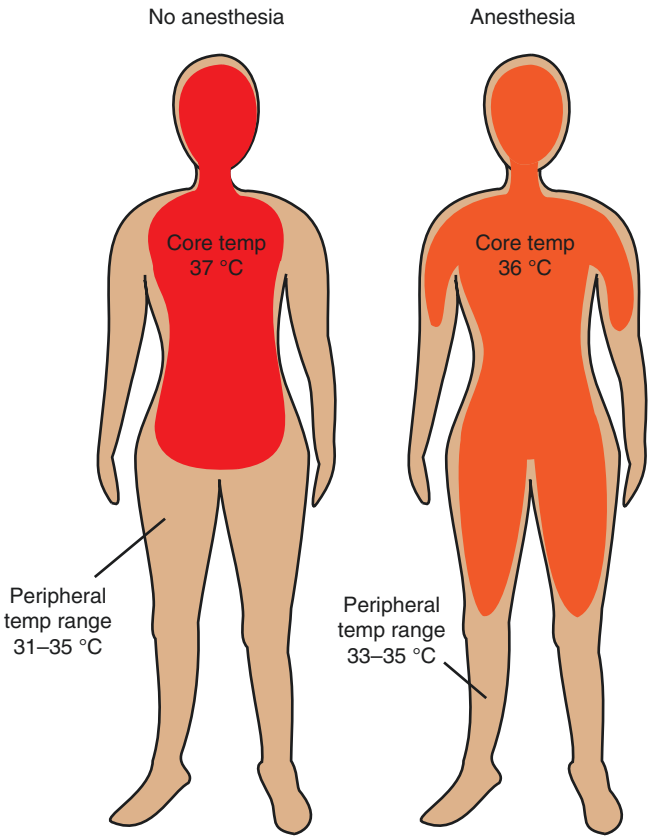

Fig. 17.1 Comparison of core body temperature: unanesthetized vs. anesthetized. (Adapted from Ref. [10])

Temperature Distribution

Classically, body heat distribution is divided between two compartments: a core (or central) compartment and peripheral (or shell) compartment (Fig. 17.1) [1, 9]. The former is much more constant in temperature, whereas the latter areas are somewhat cooler, with temperature varying much more to ensure core temperature stability. In the early stage of surgery, there is redistribution of core heat to the periphery; later there is a phase of linear heat loss. Finally, the plateau phase occurs, when the peripheral vasoconstriction threshold is triggered to limit further heat loss [4].

Temperature Measurement

An accurate measurement of core temperature is vital for patients undergoing major surgery. "True" core measurements may be obtained from pulmonary artery catheter (almost obsolete), nasopharynx at 10–20 cm depth, esophagus, and tympanic membrane [2]. However, for some patients these may not be practical, and other methods are therefore used such as axillary, urinary catheter, rectal, and skin temperature measurements. All methods have their limitations. A commonly used method is skin temperature, which is a peripheral measurement, and this may include an algorithm that adds a constant to allow an assessment of core temperature. More recently, the zero heat-flux (deep forehead) thermometry has been popularized and is recommended, with more than 500 patients from 7 studies confirming its reliability [10, 11]. This is a noninvasive measurement of core body temperature with a reported accuracy of ±0.2 °C between 31 and 37 °C [12, 13].

Maintaining Normothermia

Temperature measurement should begin preoperatively and continue well into the postoperative period. Induction of anesthesia should not commence if the patient's temperature is <36 °C, and they should receive active warming if from the start of the procedure the duration of anesthesia is expected to be >30 minutes [10].

There are many methods described to prevent perioperative hypothermia. These include passive insulation, ensuring the ambient temperature should be at least 21 °C while the patient is exposed and prior to active warming starting [10],

warming of intravenous (IV) and any irrigation fluids (particularly if administered in volumes in excess of 1 liter/hour), warming and humidification of anesthetic gases, and, most importantly, body warming devices.

Intravenous fluid warming is usually undertaken with an in-line fluid warmer, with irrigation fluids warmed in a warming cabinet. A Cochrane review of the effects of warming IV and irrigation fluids analyzed 24 studies and 1250 participants. While warmed IV fluids kept the patient about 0.5 °C warmer perioperatively and reduced shivering, there was no demonstrable benefit for warming irrigation fluids. In addition, the authors questioned how clinically meaningful these results were when other methods were used alongside as there is likely to be a ceiling effect [14]. Nevertheless, warming of both intravenous and irrigation fluids is widely regarded as a standard of care to prevent IPH.

Forced-air body warming devices have become a key area in the prevention of IPH. The large surface area of the skin provides an efficient and safe way for these devices to both transfer heat to the body and reduce heat losses. This occurs in relation to the body surface area covered, so that lower body blankets and surgical access blankets provide improved temperature control compared to upper body blankets alone. Great care must be exercised to minimize accidental thermal injury to patients and the correct use of antimicrobial filters to prevent infection. Other types of body warming devices include resistive heating (a low-voltage electric current passed through a semiconductor, thus generating heat). Generally, these devices may provide broadly similar results to forced-air warming devices but have the potential to be cheaper, more energy efficient, and quieter. Circulating water mattresses are less efficient than forced-air body devices, but circulating water garments are very efficient at achieving higher core temperatures. Finally, negative-pressure water warming devices, by improving skin perfusion and mechanically distending subcutaneous blood vessels, may prove to be useful too [15].

In addition, attention has focused on warmed and humidified CO_2 used for insulation for patients undergoing laparoscopic surgery, which may contribute to hypothermia. Demonstrated to be moderately effective, a recent meta-analysis of 13 studies showed that the use of warmed and humidified CO_2 was associated with a significant increase in intraoperative core temperature (mean change 0.3 °C) [16]. However, a more detailed Cochrane review looked at 22 studies with 1428 participants and, while confirming the preservation of temperature and demonstrating a reduced post-anesthesia care unit (PACU) stay, commented that the data was heterogeneous and when low-risk-of-bias studies only were included, the PACU stay was not significantly reduced [17]. As there was no improvement in patient outcome as well as other areas such as a reduction in lens fogging, its use was not supported [18].

Prewarming

A logical area to minimize IPH is the use of prewarming. Recent reviews supported this idea, with significantly higher temperatures demonstrated perioperatively [18, 19] unless this would delay emergency surgery, although the practicalities of this may not be easy to overcome. It is superior in combination with intraoperative warming, compared to intraoperative forced-air warming alone [6].

Conclusion

Reliable core temperature monitoring should be undertaken in all patients undergoing major surgery or surgery expected to be in excess of 30 minutes, and methods to actively warm patients to avoid IPH should be employed. Particular attention should be paid to patients at higher risk of IPH or its sequelae, including American Society of Anesthesiologists (ASA) class 2–5 patients, those with preoperative hypothermia, those undergoing combined regional and general anesthesia and major surgery, and those at risk of cardiovascular complications [10].

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Perioperative Intravenous Fluid Therapy in ERAS Pathways

18

Katie E. Rollins and Dileep N. Lobo

Introduction

Perioperative fluid management has been identified as one of the key components of enhanced recovery after surgery (ERAS) pathways, with excessive fluid administration associated with increased morbidity [1–3] and mortality [4] over a range of surgical specialties. The aims of ERAS pathways are to minimize surgical stress, maintain normal physiological function, and optimize patient recovery after surgery [5, 6]. Excessive fluid administration results in interstitial tissue edema, reduced gastrointestinal function, and impaired anastomotic healing, whereas sub-optimal fluid resuscitation results in tissue hypoperfusion and hypoxia, which can also result in reduced postoperative gastrointestinal function and anastomotic complications [3, 7]. Previous evidence has demonstrated that the administration of every additional individual liter of intravenous fluid on the day of surgery results in a 16% increased risk of postoperative symptoms delaying recovery from surgery and a 32% increase in postoperative morbidity [8]. The aim of this chapter is to provide an overview of the evidence with particular relevance to the published consensus statements and guidance specific to the perioperative infusion of intravenous fluid as part of an ERAS pathway [9, 10].

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Preoperative Fluid Therapy

In an ERAS pathway, the importance of reaching the anesthetic room in a hydrated, euvolemic state with correction of any electrolyte imbalances is emphasized. This is mostly achieved by minimizing preoperative starvation periods, as per current guidance [11, 12], of 6 hours for solid food and 2 hours for clear fluids including carbohydrate drinks and avoidance of mechanical bowel preparation (MBP) to reduce the incidence of preoperative fluid and electrolyte deficits. A Cochrane systematic review and meta-analysis of 38 randomized controlled trials (RCTs) [13] found that a shortened fluid fast did not significantly alter the incidence of aspiration, regurgitation, or related postoperative morbidity when compared with starvation from midnight prior to surgery. Historically, prolonged fasting was recommended to reduce the incidence of pulmonary aspiration and associated morbidity and mortality; however, this has been documented as a risk of approximately 1 in 7000, 1 in 1700, and 1 in 100,000, respectively [14]. (See Chap. 4)

The concept of oral carbohydrate loading remains a controversial topic, despite good basic science evidence that this intervention reduces perioperative insulin resistance, which results in increased glucose levels, hyperglycemia, and decreased glycogen storage, which can lead to muscle degradation [15]. A carbohydrate load has been shown to convert the metabolic state of the patient from fasting to fed, and evidence suggests that this is safely tolerated up to 2 hours prior to induction of anesthesia. Despite this good body of evidence, the benefits associated with carbohydrate loading in the clinical setting have not proven as conclusive [16–19]. (See Chap. 4)

MBP is historically associated with large fluid and electrolyte losses [20, 21] and patient dissatisfaction [22], and there are large meta-analyses that support a lack of clinical benefit associated with MBP alone [23, 24]. The topic of MBP in combination with oral, nonabsorbable antibiotics (OAB) therapy is currently very much in flux. There is increasing evidence that the combination of MBP and OAB is associated with a significant reduction in the risk of

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surgical site infection and possibly anastomotic leak rates [25, 26]. However, modern, isosmotic mechanical bowel preparations are associated with reduced physiological consequences when compared with older hyperosmotic solutions [27] as they do not induce a shift in fluid toward the bowel lumen. MBP in the form of polyethylene glycol and OAB can be successfully administered as part of an ERAS pathway [28] without deleterious effects, so this remains a topic up for debate. The current practice for preoperative fluid therapy in ERAS pathways aims to avoid intravenous infusion unless this is absolutely necessary to render the patient euvolemic prior to anesthetic. A study comparing preoperative fluid management in patients undergoing elective colectomy within an ERAS pathway versus traditional care found those managed within an ERAS pathway were significantly less likely to be fluid responsive following induction of anesthesia [29].

Intraoperative Fluid Therapy

In the setting of ERAS pathways, intraoperative fluid therapy aims to optimize cardiac function, tissue perfusion, and intravascular volume without creating fluid and salt overload, which is associated with prolonged hospital length of stay (LOS), postoperative morbidity, and delay in return of gastrointestinal function. This cardiovascular optimization should be achieved using an individualized approach rather than a proscriptive, one-size-fits-all methodology. Generally, intraoperative fluid therapy aims for near-zero-balance of both water and salt content and is based on maintenance fluid infusion in combination with "fluid challenges" to guide additional fluid replacement. The aim of infusion of maintenance fluid is to replace direct losses from the body in the form of diuresis and both sensible and insensible losses. In major abdominal surgery, insensible losses are elevated, with evidence estimating these to be approximately 0.5–1 ml/kg/h [30], although this varies greatly according to the degree of exposure of the viscera to the operating room environment. The typically quoted figure for infusion of maintenance fluid is 1–3 ml/kg/h and is generally provided as a balanced crystalloid solution to minimize salt overload [31]. Excessive intraoperative fluid administration results in damage to the endothelial glycocalyx, release of atrial natriuretic peptides, and elevated intravascular hydrostatic pressure [32], with resultant impaired gastrointestinal function and increased postoperative morbidity. On the other hand, inadequate intraoperative fluid therapy of just 10–15% of the circulating blood volume results in a documented fall in perfusion of the splanchnic circulation, and this hypoperfusion frequently outlasts the period of hypovolemia [33]. Splanchnic hypoperfusion then leads to mucosal acidosis [34] and impaired gastrointestinal function, increased rates of anastomotic complications, and postoperative morbidity [35]. Therefore, a near-zero-balance approach to intraoperative fluid therapy is key to optimizing postoperative outcomes.

The most commonly utilized method to guide intraoperative fluid bolus therapy is with goal-directed fluid therapy (GDFT), which uses "fluid responsiveness" to a set fluid bolus, typically 200–250 ml, to guide ongoing fluid therapy. This aims to optimize the patient's stroke volume on their individual Frank-Starling curve. An improvement in stroke volume exceeding 10% indicates the requirement for an additional fluid bolus, whereas responsiveness less than 10% suggests adequate cardiac contractility and optimization, and that maintenance of the background fluid infusion is currently sufficient. This method uses hemodynamic monitoring, which can be performed in a number of ways such as transesophageal Doppler, lithium dilution techniques, corrected flow time, and stroke volume variation monitoring. The evidence for GDFT is currently mixed. Evidence from a number of randomized controlled trials [36] initially suggested a statistically significant benefit in terms of hospital length of stay and postoperative morbidity rates, which led to this technology being recommended as a standard of care by the UK National Institute for Health and Care Excellence (NICE) [37]. However, several meta-analyses have cast doubt upon the perceived benefits of GDFT in perioperative fluid management [38–40], particularly when administered as part of an ERAS pathway [41]. A recent meta-analysis including 23 studies has generated interesting results [41]. Overall, GDFT was associated with a significant reduction in morbidity (risk ratio [RR] 0.76, 95% confidence interval [CI] 0.66 to 0.89, $p = 0.007$), hospital LOS (mean difference −1.55 days, 95% CI −2.73 to −0.36, $p = 0.01$), and time to passage of feces (mean difference −0.90 days, 95% CI −1.48 to −0.32 days, $p = 0.002$). However, no difference was seen in mortality, return of flatus, or incidence of postoperative ileus. If patients were managed within an ERAS pathway, the only significant reductions were in intensive care LOS (mean difference −0.63 days, 95% CI −0.94 to 0.32, $p < 0.0001$) and time to passage of feces (mean difference −1.09 days, 95% CI −2.03 to −0.15, $p = 0.02$). If managed in a traditional care setting, a significant reduction was seen in both overall morbidity (RR 0.69, 95% CI 0.57 to 0.84, $p = 0.0002$) and total hospital LOS (mean difference −2.14, 95% CI −4.15 to −0.13, $p = 0.04$). Emerging evidence has suggested that GDFT may be more beneficial in high-risk patient populations [42]. However, this is yet to be well established, with a large, multicenter, randomized controlled trial [43] recruiting 734 high-risk patients undergoing major gastrointestinal surgery comparing cardiac output-guided hemodynamic therapy demonstrating no significant difference in the incidence of a composite outcome of 30-day moderate or major complications and mortality (relative risk [RR] 0.84, 95% CI 0.71 to 1.01). However,

when these data were included within a systematic review and meta-analysis within the same paper, the intervention was associated with a significant reduction in the incidence of complications (RR 0.77, 95% CI 0.71 to 0.83) but a nonsignificant reduction in hospital or 30-day mortality. A consensus statement has been produced by the Enhanced Recovery Partnership [10], which recommends that perioperative fluid therapy should by individually tailored to the patient, anesthetist, and surgical procedure dependent upon risk. However, they provide a list of cases in whom GDFT should be provided from the outset, including major surgery with a 30-day mortality exceeding 1%; major surgery with anticipated blood loss exceeding 500 ml; and major intra-abdominal surgery and intermediate surgery, described as cases with a mortality rate exceeding 0.5% in high-risk patients, classified as those aged over 80 years or those with a history of left ventricular failure, myocardial infarction, stroke, or peripheral arterial disease. This is further reinforced by the American Society for Enhanced Recovery (ASER) and Perioperative Quality Initiative (POQI) joint consensus on perioperative fluid therapy within an ERAS pathway for patients undergoing colorectal surgery [9]. This weighs up the fact that although GDFT is unlikely to be associated with any significant risk to patients, it is associated with a not insignificant cost. The suggestion of this consensus is that minimally invasive cardiac monitoring devices may be utilized dependent upon patient- and procedure-specific risks.

A proposed alternative to GDFT is that of aiming for "near-zero fluid balance" as initially proposed by Brandstrup et al. [44] who found that in a randomized controlled trial, restrictive intravenous fluid administration that aimed for zero weight gain versus standard intravenous fluid resulted in a significant reduction in postoperative complications (33% versus 51%, $p = 0.014$) and cardiopulmonary complications (7% versus 24%, $p = 0.007$), with no harmful adverse effects observed. Furthermore, several studies have compared GDFT versus zero-balance fluid therapy and have demonstrated no difference in postoperative surgical outcomes [29, 45]. The recently published "Restrictive versus Liberal Fluid Therapy for Major Abdominal Surgery" (RELIEF) trial [46] compared restrictive and liberal fluid therapy intraoperatively to 24 hours post-op in patients undergoing major abdominal surgery at high risk of complications, finding that restrictive therapy was associated with a significantly increased risk of acute kidney injury (8.6% vs. 5.0%, $p < 0.001$) as well as requirement for renal replacement therapy (0.9% vs. 0.3%, $p = 0.048$). This did not result in a difference in the primary outcome measure of disability-free survival at 1 year (81.9% vs. 82.3%, $p = 0.61$).

The Enhanced Recovery Partnership has created a list of aims of fluid management for the end of surgery [10], as detailed in Table 18.1.

Table 18.1 Aims of enhanced recovery-based fluid management – from the Enhanced Recovery Partnership consensus statement [10]

Patient's core temperature is normal (circa 37 °C)
No evidence of hypovolemia, tissue hypoperfusion, or hypoxia
No evidence of hypervolemia or excess fluid ("zero balance")
Hemoglobin ≥70 g/L
No clinically significant coagulopathy
Minimal use of vasopressors

Postoperative Fluid Therapy

In the postoperative setting, within an ERAS pathway, patients should be encouraged to commence oral fluid intake followed by solid food as soon as possible, typically the day after surgery. If the patient is able to tolerate oral intake, intravenous fluid supplementation should be discontinued, with it being restarted only if clinically indicated. In the absence of excessive surgical losses but a requirement for maintenance fluid, a physiological fluid infusion should be administered, at a rate of 25–30 ml/kg per day with less than 70–100 mmol sodium per day, along with potassium supplements [47]. If this volume is not exceeded, hyponatremia is very unlikely to occur [48, 49]. Any ongoing losses such as excessive vomiting, high nasogastric (NG) drainage, or high stoma losses should be replaced on a like-for-like basis for what is being lost in addition to the maintenance requirement. Evidence originating from centers that do not continue "maintenance" fluid therapy once the patient is able to tolerate independent oral intake has demonstrated this to be associated with a significant reduction in hospital length of stay [50]. The aim of postoperative fluid therapy is to maintain the patient in as near a state of zero-balance as possible, both in terms of fluid volume and electrolyte balance. Electrolyte balance is a particular issue in the postoperative setting due to evidence of impaired sodium and chloride excretion following surgery [48]. It has been hypothesized that postoperative morbidity has a U-shaped relationship to postoperative fluid volumes infused [51]. A meta-analysis that compared "fluid balance" versus "imbalance" perioperative fluid therapy in patients undergoing elective open abdominal surgery [2] found those in the "balanced" group developed fewer complications (RR 0.59, 95% CI 0.44 to 0.81, $p = 0.0008$) and had an overall shorted hospital length of stay (weighted mean difference −3.44, 95% CI −6.33 to −0.54, $p = 0.02$).

Postoperative analgesia in the ERAS setting is frequently provided in the form of a thoracic epidural (TEA). However, TEA is associated with cardiodepressant effects as well as arterial and venous vasodilatation [52], both of which result in hypotension as a consequence of "relative hypovolemia" due to circulating volume redistribution. Careful thought must be given to the patient's fluid balance status, as euvolemic patients with a TEA who are hypotensive will not benefit from additional fluid therapy [53], and this runs the

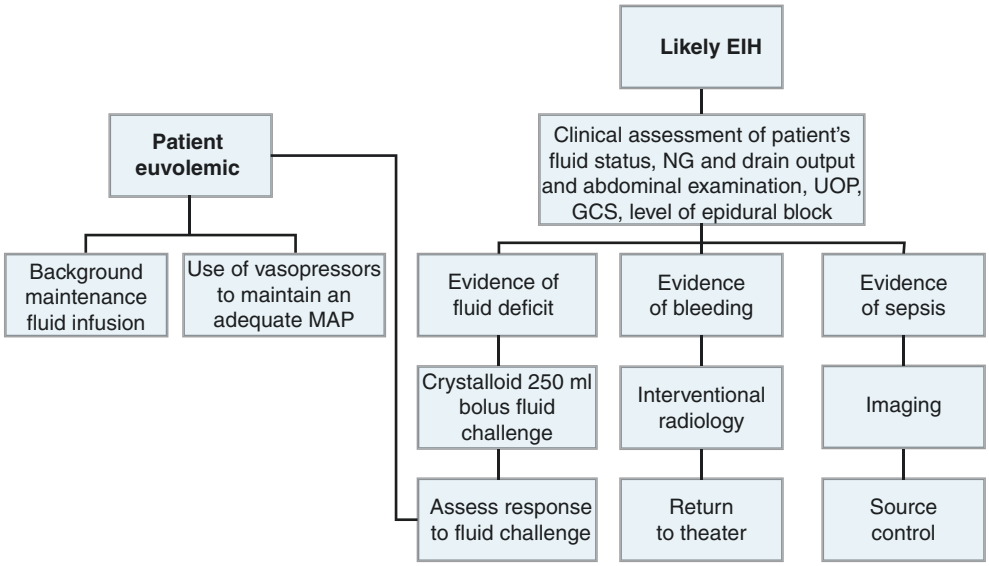

Fig. 18.1 Suggested flowchart for the management of postoperative epidural-induced hypotension (EIH). Abbreviations: NG nasogastric, UOP urine output, GCS Glasgow Coma Scale, MAP mean arterial pressure

risk of fluid overload and the resultant increased incidence of postoperative morbidity. The management of TEA-related hypotension should include consideration of slowing the rate of the TEA as well as low-dose catecholamine infusion to reduce sympathetic blockade and improve intravascular tone (Fig. 18.1).

Urine Output

There is good evidence to support the assertion that intraoperative oliguria, defined as <0.5 ml/kg/h [54] or <500 ml in a 24-hour period, is a normal physiological "stress" response to both anesthesia and surgery, which results in retention of salt and water for the maintenance of intravascular volume. This is particularly common in the first 48 hours following surgery. Therefore, the presence of intra- and early post operative oliguria in isolation should not trigger fluid administration, particularly in the absence of other signs of tissue hypoperfusion such as tachycardia, hypotension, low central venous pressure, and capillary refill time. Careful clinical assessment of the patient's fluid status is key to the management of postoperative oliguria and should be undertaken in a serial manner rather than a static assessment. The use of invasive cardiovascular monitoring such as a CVP line and urinary catheter may also assist in the assessment of fluid balance. Excessive fluid administration in a patient who is oliguric but not in a state of fluid deficit results in expansion of the circulating blood volume as well as the interstitial fluid volume. The metabolic response to surgery also results in an impaired ability to excrete sodium, thus exacerbating the expanded interstitial fluid volume and resulting in increased postoperative morbidity. The management of a postoperative surgical patient with oliguria is governed by repeated clinical assessment, fluid resuscitation if indicated, and assessment of the cause for oliguria (Fig. 18.2). It should be noted, however, that anuria is always pathological until proven otherwise and should always be taken seriously.

A recently published post hoc analysis of the RELIEF (Restrictive Versus Liberal Fluid Therapy for Major Abdominal Surgery) trial [55] demonstrated that in a cohort of 2444 patients, intraoperative oliguria had a low predictive value for acute kidney injury (AKI). This adds further weight to a meta-analysis of 15 studies that found that intraoperative fluid restriction was associated with an increased incidence of oliguria, but not in the incidence of AKI [56]. More recent studies advocate increasing the threshold for diagnosis of oliguria to 0.3 ml/kg/h, suggesting that this level has a stronger association with the incidence of AKI [57].

Types of Fluid

Much research has been conducted into the best solution for perioperative infusion in terms of both maintenance and to a lesser degree bolus fluid. The infusion of large volumes of 0.9% saline has been demonstrated to be associated with hyperchloremic acidosis due to its supranormal levels of both sodium and chloride, which appears to affect renal function adversely due to a reduction in urinary water and sodium excretion resulting in reduced renal blood flow, 30-day mortality, and prolonged hospital length of stay [58]. A recent cluster-randomized, multiple-crossover trial conducted in critically unwell patients [59] comparing infusion of balanced crystalloids versus saline found that the balanced group had a lower rate of the composite outcome of death from any cause, new renal replacement therapy, or persis-

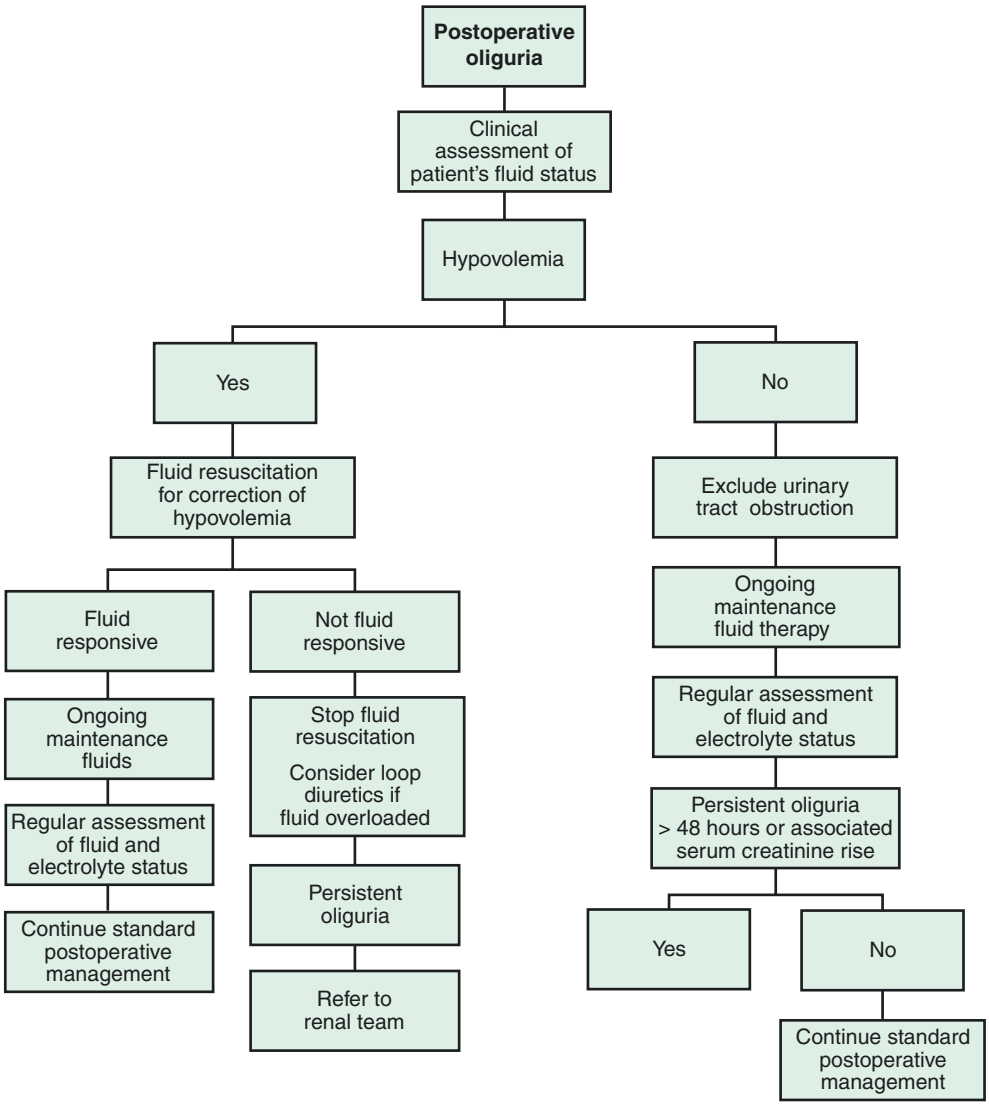

Fig. 18.2 Management of a postoperative surgical patient presenting with oliguria

tent renal dysfunction. However, a similar trial conducted in noncritically unwell adult patients receiving intravenous fluid therapy in the emergency department found no difference between those receiving balanced crystalloids and saline in hospital-free days—although balanced crystalloids were associated with a significant reduction in the incidence of major adverse kidney events occurring within 30 days of admission (4.7% vs. 5.6%, adjusted odds ratio 0.82, 95% CI 0.70 to 0.95, $p = 0.01$). Specific to the surgical literature, a recent meta-analysis of nine RCTs in adult patients undergoing nonrenal surgery found that patients in the saline group had a significantly lower postoperative pH (mean difference 0.05; 95% CI: 0.04 to 0.06; $p < 0.001$; $I^2 = 82\%$) and base excess (mean difference 2.04; 95% CI: 1.44 to 2.65; $p < 0.001$; $I^2 = 87\%$) as well as a significantly higher chloride level (mean difference −4.79; 95% CI: −8.13 to −1.45; $p = 0.005$; $I^2 = 95\%$) [60]. A recent double-blind comparison of normal saline versus balanced crystalloids [61] in patients undergoing major abdominal surgery found that normal saline was associated with an increased risk of vasopressor support (97% versus 67%, $p = 0.033$) but no difference in the rate of unplanned intensive care unit admissions. Hence, there has been increasing focus upon the use of more "balanced" crystalloid solutions in both the maintenance and bolus setting.

In terms of the intraoperative fluid of choice for bolus administration, historically colloids were utilized most frequently due to their perceived benefit in terms of intravascular fluid expansion. However, increasing evidence surrounding the fluid of choice for bolus administration has suggested no significant benefit of colloids over balanced crystalloid solutions [62–64]. Many of the initial studies surrounding GDFT utilized synthetic colloids, most commonly hydroxyethyl starch (HES); however, there is currently a moratorium placed upon the use of HES due to three studies originating from the critical care literature that suggested HES was associated with a significantly increased risk of renal replacement therapy or mortality [65–67].

Conclusion

Perioperative fluid therapy within an ERAS setting is a key determinant of surgical outcome. Delivery of the patient to the anesthetic room in a hydrated, euvolemic state combined with a careful zero-balance approach to water and salt administration in the intra- and postoperative setting and judicious use of goal-directed fluid therapy in high-risk patient or procedure groups are all key to optimizing patient outcomes. The literature currently supports the increasing administration of balanced crystalloids over colloids or unbalanced crystalloids; however, this is not incontrovertibly established.

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ERAS and Minimally Invasive Surgical Techniques

19

Daniel White and Timothy A. Rockall

Introduction

Enhanced recovery after surgery (ERAS) is a well-established multimodal pathway of perioperative care that has been proven to improve the quality of recovery, reduce complications, and reduce length of hospital stay (LOS) in many areas of surgery. Simultaneous with the introduction of ERAS pathways have been the introduction and expansion of minimally invasive techniques (MIS) for surgery that in many cases have become standard practice. These minimally invasive techniques have become embedded in many ERAS protocols because of the obvious benefits in reducing access trauma, reducing pain and therefore requirement for opiate analgesia, minimizing fluid shifts, and reducing complications such as ileus, blood loss, pulmonary complications, and wound infections. Minimally invasive surgery is both an important pillar of ERAS in many specialties and an enabler of many of the other components of ERAS such as fluid management, analgesia, and mobilization. The multimodal nature of ERAS protocols means that it is not always possible to demonstrate that individual components result in significant patient benefit, even when increased compliance overall is associated with better outcomes. Minimally invasive surgery, however, is consistently an independent factor for improved outcome. Minimally invasive surgery and ERAS methodology can be seen as synergistic methods of optimizing outcomes after surgery.

In some specialties, there are an increasing number of different techniques and different technologies evolving to achieve a minimally invasive approach. In some cases, they may promote or enable a minimally invasive technique where traditional laparoscopic techniques are considered difficult to learn, have a high conversion rate, or are not widely applicable. They may therefore be considered as enabling technologies to allow wider adoption of minimally invasive surgery. In other circumstances, new technologies or techniques attempt to reduce the number or size of ports required, thus reducing access trauma even further. And in some circumstances, they are promoted as methods of improving dexterity and precision and thus improve specimen quality and reduce complication rates. In reality, there is very little evidence in any field of superiority of one minimally invasive surgical technology over another. When subjected to randomized controlled trials (RCTs) and in the context of ERAS, the important element is probably the avoidance of open surgery rather than the use of any specific minimally invasive technique. The aim of this chapter is to provide a broad cover on the application of MIS across the various specialties and explore the evidence of the potential benefits of MIS toward attenuation of surgical stress response within the context of ERAS.

Background to Minimally Invasive Surgery

The widespread introduction of laparoscopy into surgery has been the singular revolutionary change in surgical technique in the last 100 years. It has transformed the way we operate and has transformed outcome and recovery for many common surgical operations. Although to many the improvements were immediately both dramatic and obvious, it did not prevent an abundance of skepticism for nearly every operation into which the technology was introduced. This prompted research including randomized clinical trials to try and prove the superiority, or more commonly a lack of inferiority, of one technique over another. It is unlikely, however, that these trials or their results really had any significant impact in slowing down the uptake of operations such as laparoscopic cholecystectomy. Other more complex operations have been introduced more gradually. With the

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evolution of robotic surgery, this pattern has re-emerged, and despite a lack of randomized trials to support the technology, in 2003 only 1.8% of prostatectomies were performed robotically, rising to 85% by 2013 in the United States and more than 5000 robotic systems currently in use [1].

Common abdominal operations such as cholecystectomy, appendicectomy, fundoplication, inguinal hernia repair, and even colorectal resection as well as less common operations such as adrenalectomy are being performed with hospital stays of less than 24 hours. There are few if any reports in the literature of this being achievable with open techniques in cholecystectomy, colorectal resection, fundoplication, or adrenalectomy.

Cholecystectomy

The first laparoscopic cholecystectomy was performed in 1987 by Mouret and is now the principal method in developed countries. An operation that was associated with significant postoperative pain and an average of 1 week in hospital has been transformed into a day case procedure for uncomplicated cases [2]. An early publication looking at 356 patients demonstrated a median stay of 3 days for laparoscopic compared to 7.5 days converted and 9.5 days open with return to work of 21 days, 42 days, and 56 days, respectively [3].

Hesitancy in the uptake of new technology is common, with concerns regarding safety, re-training, surgical outcomes, and costs. Hesitancy for cholecystectomy was more related to the apparent rise in bile duct injury than any real doubt surrounding its ability to improve recovery. Some authors questioned its superiority over the concept of "mini" or "small incision open" cholecystectomy, but a randomized controlled trial of laparoscopy versus mini laparoscopic cholecystectomy as early as 1994 showed a hospital stay reduction of 2 days, return to work reduced by 1 week, and similar complications in each group [4]. A systematic review showed that both laparoscopic and mini cholecystectomy were better than open but was unable to differentiate outcomes between laparoscopic and mini cholecystectomy [5]. A meta-analysis of mini cholecystectomy and laparoscopic cholecystectomy including 2032 cases revealed similar outcomes and a reduced hospital stay of 0.37 days [6]. The wound infection rate in open cholecystectomy was three times that of the laparoscopic approach. A Cochrane review of 38 trials including 2338 cases comparing open and laparoscopic revealed a 3-day shorter hospital stay and reduced convalescence time with no significant differences in mortality, complications, or operative time. It does appear that mini cholecystectomy can be performed with similar results to laparoscopic cholecystectomy, but while laparoscopy is a suitable technique for patients with even the most challenging body habitus, mini cholecystectomy can be difficult and not universally applicable.

The vast majority of cholecystectomy operations are undertaken using standard laparoscopic techniques with three or four ports. Other methods of minimally invasive cholecystectomy such as single-incision laparoscopic surgery (SILS) or natural orifice transluminal endoscopic surgery (NOTES) have been introduced. However, few complex NOTES cases have been performed, with no rigorous studies, and the main consensus is that although enthusiasm for the concept is high, the technical restrictions and abilities of the equipment and platform negate major use for anything other than very basic procedures. It can be concluded that there are no adequately powered studies to assess the safety of these techniques, and evidence would suggest that for SILS the time taken is longer, the blood loss is greater, and the failure rate is significant, although some authors have reported an improved quality of life for single-incision laparoscopic surgery [7, 8]. Randomized trials in this area are sparse, with one published RCT showing equivalence of robotic and four-port technique, with one other still recruiting [9]. Retrospective data have thus far shown no advantages of robotic surgery in cholecystectomy but have again shown elevated costs. A meta-analysis of robotic cases compared to standard 4-port technique comprising 1400 cases did show equivalence in the 2 methods [10].

Colorectal Resection

Colorectal surgery has been introduced into mainstream practice at a much slower rate than, for example, cholecystectomy despite the first operations being performed as early as 1991. This is a reflection of its complexity, a lack of laparoscopic skills among traditionally open colorectal surgeons, concerns about oncological safety, and undoubted resistance from an establishment of conservative surgeons. Prior to the introduction of laparoscopic surgery, hospital stay following colorectal resection in the United Kingdom was 12.8 days on average. Length of stay for selected patients has been reported as low as 23 hours in the United Kingdom, with further randomized trials, such as RecoverMI, planned to assess the safety of a 23-hour discharge [11, 12]. There were a number of trials, such as CLASICC, COST, and COLOR, that were in many ways imperfect but nevertheless served to demonstrate a lack of disadvantage – oncological or otherwise. The contrary is in fact demonstrated with both COLOR II and work by Day et al. showing a possible survival advantage to laparoscopic surgery [13–15]. The largest trials reporting a failure to achieve non-inferiority of laparoscopic surgery compared to open are ACOSOG Z0651 and ALaCaRT [16, 17].These studies used a composite measure of quality, using positive circumferential margins, distal margin negativity, and completeness of total mesorectal excision (TME). They have reported their survival outcomes showing that although histologically there seemed to be a concern,

Table 19.1 Trials comparing laparoscopic and open surgery

Name	Population	Design	Primary outcome	Findings
ACOSOG Z0651	Stage 2/3 rectal cancer, all neoadjuvant therapy *n* = 486	Non-inferiority RCT	CRM <1 mm, distal margin <1 mm, TME completeness	2015 – open resection superior for primary outcome. Non-inferiority NOT demonstrated 2018 – no significant difference in DFS and recurrence rates
ALaCaRT	T1–T3 rectal adenocarcinoma within 15 cm of anal verge *n* = 475	Non-inferiority RCT	CRM < 1 mm, distal margin <1 mm, TME completeness	2015 – non-inferiority not demonstrated Long-term results awaited
CLASICC	Colorectal cancer including rectal cancer (excluding transverse colon tumors only) *n* = 794	RCT	Circumferential, longitudinal, and high-tie mesenteric resection margins 3-year disease-free survival, OS and local recurrence	Laparoscopic surgery safe compared to open surgery Unable to support use of laparoscopic surgery Higher CRM positivity in laparoscopic group ($p = 0.45$) Not significant
COLOR 1	Colorectal cancer (excluding tumors below peritoneal reflection) *n* = 627	RCT	3-year cancer-free survival	Earlier recovery of bowel function (−1.0 days), less analgesia, shorter LOS (−1.1 days), less blood loss (175 ml vs 100 ml) No difference in overall morbidity or mortality
COLOR 2	Rectal cancer (Tumor within 15 cm of anal verge) *n* = 1044	Non-inferiority RCT	Locoregional recurrence at 3 years	Disease-free survival (74.8% vs 70.8%) and overall survival (86.7 vs 83.7%) higher in laparoscopic group Non-inferiority demonstrated
COREAN	T3 N0–N2, rectal cancer without metastases. All underwent neoadjuvant therapy *n* = 340	Non-inferiority RCT	3-year cancer-free survival	Involvement of the circumferential resection margin did not differ between groups

RCT randomized controlled trial, *CRM* circumferential margin, *TME* total mesorectal excision, *DFS* disease-free survival, *OS* overall survival, *LOS* hospital length of stay

this did not translate into any oncological/survival disadvantage at 3 years. A summary of pertinent trials is provided in Table 19.1.

Initial National Institute for Health and Care Excellence (NICE) guidance published in 1999 on this health technology determined that laparoscopic surgery for colorectal cancer should not be performed in the United Kingdom unless patients were being recruited to a trial (CLASICC was recruiting at that time). This reflected a lack of evidence in its favor at that time. The technology was revisited in 2006 when all the available evidence was reassessed, and the guidance published at that time was that laparoscopic surgery should be offered to suitable patients with colorectal cancer on the basis of patient benefit and minimal health economic disadvantage. There was recognition at that time that certainly in the United Kingdom the volume of surgery could not be delivered by suitably trained surgeons, and so adherence to the guidance was waived for a total of 4 years during which time there was significant investment into laparoscopic training [18].

As technology has advanced, robotic surgery and transanal surgery have entered the debate. Robotic colorectal surgery with the Intuitive DaVinci system was first performed as early as 2001 and described in the literature in 2003 [19]. Similarly to the evolution of laparoscopic surgery, robotic surgery has its critics. Concerns seemed validated by early review in the United States showing that the majority of work was done in low-volume centers, leading to higher complication rates, longer lengths of stay, increased costs, and poorer oncological outcomes [20]. More recently a UK review concluded that for right hemicolectomy, rectal cancer, and ventral mesh rectopexy, there are potential, as yet unproven advantages. Performing an intracorporeal anastomosis for right hemicolectomy may allow a smaller incision with reduced risk of incisional hernia and less pain and possibly provide a higher lymph node yield. A meta-analysis of seven studies in 2017, containing just one randomized study, demonstrated equivalent LOS, lower blood loss (an insignificant 19 ml), elevated costs, and elevated operating time, despite not including setup time, which is a major component to consider [21]. Further trials are ongoing, but no superiority has been demonstrated over laparoscopic methods.

Some believe there is a stronger case for robotics in rectal cancer surgery because of the technical challenges of

operating in a narrow pelvis and the oncological importance of producing a high-quality specimen while minimizing collateral damage. A 2018 review reporting outcomes from 14 retrospective studies and case-matched series with more than 22000 cases of robotic rectal surgery concluded lower conversion rates, improved TME specimen quality with fewer positive circumferential margins (CRM), and shorter lengths of stay [22]. Despite the perceived oncological advantages, no benefit in disease-free or overall survival has been demonstrated. ROLARR, one of the few well-run multicenter randomized studies comparing laparoscopic and robotic surgery, reported in 2017 concluding no advantage from robotic surgery [23]. While there remains a debate regarding the role of robotics in rectal cancer, there remains no high-quality evidence to substantiate its widespread adoption and in particular no evidence that it contributes to the recovery of the patient within ERAS over standard laparoscopic surgery [24].

Several systematic reviews of the transanal approach to rectal cancer reveal no difference in specimen quality or anastomotic leak rates compared to laparoscopic and open surgery [25–28]. A large prospective registry of cases has revealed anastomotic failure rates and specimen quality not dissimilar to databases of standard laparoscopy [29]. A randomized trial for the transanal approach (COLOR III) has been initiated [30]. Again there is no evidence that the approach contributes to better recovery after surgery.

Upper Gastrointestinal Cancer

Entering both thoracic and abdominal cavities to perform complex surgery on the foregut leads to a large systemic inflammatory response and so minimizing the surgical insult has an important potential role in ERAS for these patients. A standard Ivor Lewis esophagectomy carries high morbidity and mortality, and the benefits of minimally invasive surgery are well demonstrated here. An open-label study showed a 20% reduction in pulmonary complications with a minimally invasive approach with no significant detriment to oncological outcomes [31]. The ROBOT trial comparing robotic-assisted minimally invasive esophagectomy (RAMIE) to open surgery has reported and shown less morbidity, namely, reduced atrial fibrillation and pulmonary complications, and significantly less pain with no oncological detriment [32]. It has been criticized, however, for a very high complication rate in both groups and a possible lack of robotic experience in the surgical cohort. Certainly, further studies are needed to justify this approach, but the potential benefit given the magnitude of the surgical insult is clear to see.

Hepatobiliary

Pancreatic surgery is a challenging minimally invasive operation. Despite a laparoscopic approach becoming the default in many areas of surgery, pancreatoduodenectomy due to its retroperitoneal location, intimate relationship with major vessels, and challenging anastomotic techniques remains an open procedure in most institutions, although a laparoscopic approach is well established in a few large-volume centers with excellent results [33]. A 2017 meta-analysis compared outcomes of laparoscopic surgery with open. From more than 3000 cases, they concluded that laparoscopic pancreatoduodenectomy is associated with less blood loss, faster postoperative recovery, shorter length of hospitalization, and no increase to operation time, but, as is often the case, the quality of data is low, and more randomized studies are needed to substantiate these findings [34]. A smaller series reviewed robotic outcomes versus open with the same conclusions [35].

Liver resection for both primary and secondary tumors, such as colorectal liver metastases, is increasingly performed with a minimally invasive approach. A meta-analysis of more than 1000 patients showed no detriment to oncological outcomes for hepatocellular carcinoma (HCC) at 1, 3, or 5 years and in fact a survival advantage for colorectal liver metastases at 3 years [36]. A consensus statement in 2015 from Japan stated that smaller surgery should now be performed by a minimally invasive approach, but larger resections remain at the discretion of the surgeon [37]. The ongoing ORANGE II trial should help this decision-making further, comparing open and laparoscopic hemihepatectomy within an enhanced recovery setting [38]. Few randomized robotic studies exist; however, a case-matched series showed a higher completion rate of pure minimally invasive surgery and lower conversion rate with robotic resection when compared to a standard laparoscopic approach. The operative time, as is common, was significantly higher in the robotic group [39].

Enhanced Recovery in the Era of Minimally Invasive Surgery

Although increasing compliance is shown to improve outcomes with respect to the multiple elements of an enhanced recovery protocol (Fig. 19.1, Table 19.2) [40], minimally invasive surgery is one of the few elements that is independently predictive of improved outcome when measured by postoperative hospital stay (Fig. 19.2a–c) [41–43]. Others include preoperative carbohydrate loading and goal-directed intravenous (IV) fluids [44]. Minimally invasive surgery is the only ERAS factor to independently demonstrate a reduction in the stress response. A review of ERAS implementation sustainability

Fig. 19.1 22 ERAS elements

Table 19.2 ERAS® Society guideline elements for colonic resections

Element	Target effect and/or comment
Preadmission	
Cessation of smoking and excessive intake of alcohol	Reduce complications
Preoperative nutritional screening and, as needed, assessment and nutritional support	Reduce complications
Medical optimization of chronic disease	Reduce complications
Preoperative	
Structured preoperative information and engagement of the patient and relatives or caretakers	Reduce anxiety, involve the patient to improve compliance with protocol
Preoperative carbohydrate treatment	Reduce insulin resistance, improve well-being, possibly faster recovery
Preoperative prophylaxis against thrombosis	Reduce thromboembolic complications
Preoperative prophylaxis against infection	Reduce infection rates
Prophylaxis against nausea and vomiting	Minimize postoperative nausea and vomiting
Intraoperative	
Minimal invasive surgical techniques	Reduce complications, faster recovery, reduce pain
Standardized anesthesia, avoiding long-acting opioids	Avoid or reduce postoperative ileus
Maintaining fluid balance to avoid over- or underhydration, administer vasopressors to support blood pressure control	Reduce complications, reduce postoperative ileus
Epidural anesthesia for open surgery	Reduce stress response and insulin resistance, basic postoperative pain management
Restrictive use of surgical site drains	Support mobilization, reduce pain and discomfort, no proven benefit of use
Removal of nasogastric tubes before reversal of anesthesia	Reduce the risk of pneumonia, support oral intake of solids

(continued)

Table 19.2 (continued)

Element	Target effect and/or comment
Control of body temperature using warm air flow blankets and warmed intravenous infusions	Reduce complications
Postoperative	
Early mobilization (day of surgery)	Support return to normal movement
Early intake of oral fluids and solids (offered the day of surgery)	Support energy and protein supply, reduce starvation-induced insulin resistance
Early removal of urinary catheters and intravenous fluids (morning after surgery)	Support ambulation and mobilization
Use of chewing gums and laxatives and peripheral opioid-blocking agents (when using opioids)	Support return of gut function
Intake of protein and energy-rich nutritional supplements	Increase energy and protein intake in addition to normal food
Multimodal approach to opioid-sparing pain control	Pain control reduces insulin resistance, supports mobilization
Multimodal approach to control of nausea and vomiting	Minimize postoperative nausea and vomiting and support energy and protein intake
Prepare for early discharge	Avoid unnecessary delays in discharge
Audit of outcomes and process in multiprofessional, multidisciplinary team on a regular basis	Control of practice (a key to improve outcomes)

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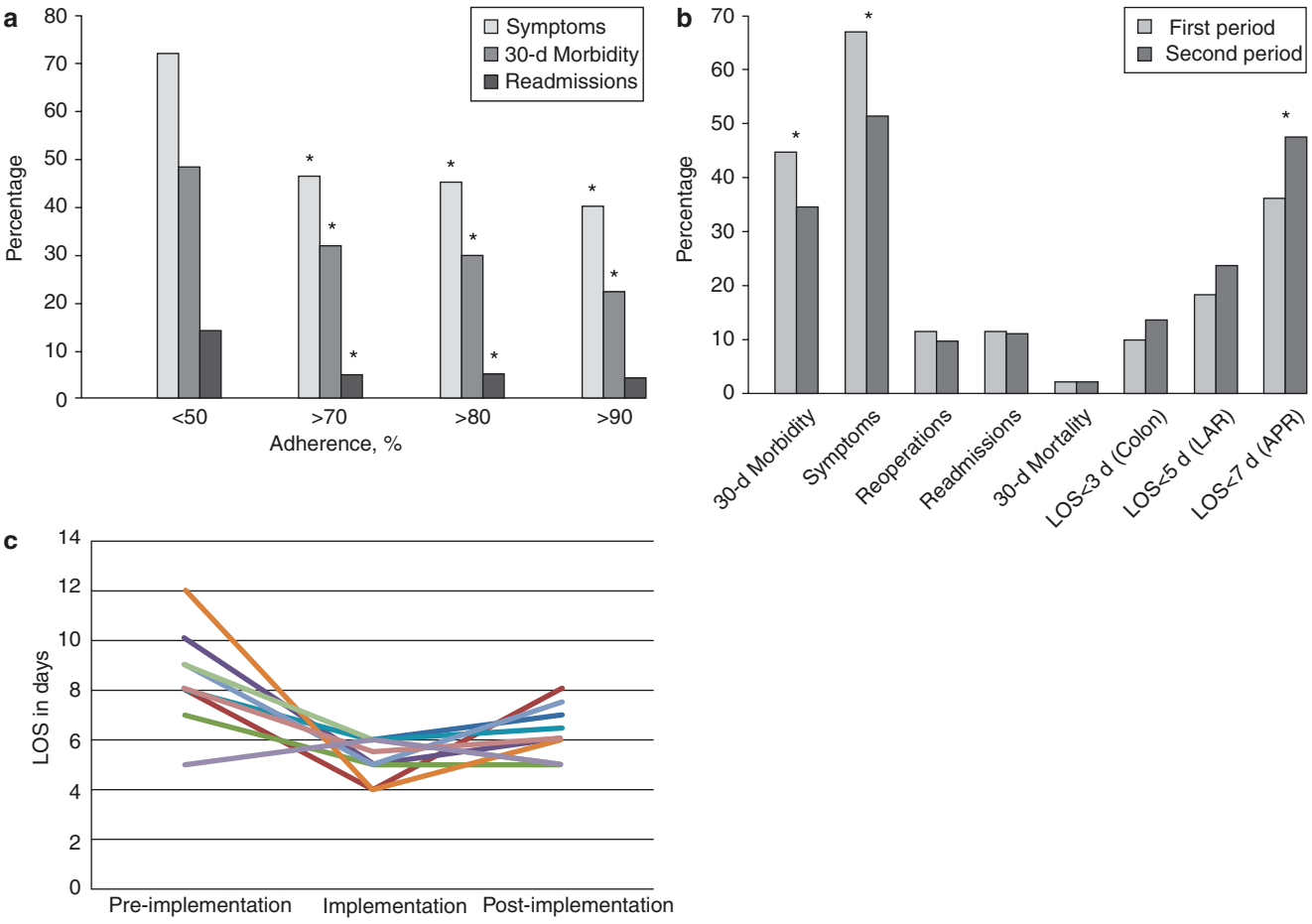

Fig. 19.2 Reductions in complications and shortened LOS with (**a**) increasing compliance (association between adherence to the enhanced recovery after surgery protocol and postoperative outcomes. ∗Statistically significant at $p < 0.05$) and (**b**) post-implementation of ERAS (APR indicates abdominoperineal resection; LAR, low anterior resection; LOS, length of stay. ∗Statistically significant at $p < 0.05$). (**a**, **b** Reprinted with permission from Gustafsson et al. [41]). (**c**) Maintenance of effects post-implementation, despite poorer compliance. Median LOS per hospital in the pre-implementation, implementation, and post-implementation phases of ERAS (2 hospitals reached the same result; those findings are shown as one line). (**c** Reproduced with permission from Gillissen et al. [43])

showed the lasting effects of ERAS implementation, as despite a slight reduction in compliance across the ten selected units, 90% of units preserved the improvements seen in postoperative outcomes. This chapter will now address the evidence for minimally invasive surgery by reviewing two trials that have been specifically designed to look at this issue of relative influence of ERAS and MIS on recovery after colorectal surgery: in the Netherlands, the LAFA trial [45], and in the United Kingdom, the EnRol trial [46].

LAFA: Perioperative Strategy in Colonic Surgery – Laparoscopy or Fast-Track Multimodal Management Versus Standard Care

The objective of this Dutch trial was to try and discern whether fast-track/enhanced recovery protocols or laparoscopic surgery or both together were the preferred management for optimal outcome after colonic resection for bowel cancer. Three research questions were posed by the trial so that hospital stay, quality of life, and cost analysis were to be made for each group.

The design was a multicenter randomized controlled trial undertaken in seven Dutch hospitals with a 2 × 2 balanced factorial design. A recruitment of 400 patients was calculated to give a greater than 95% chance of detecting a hospital stay reduction of 1 day. Adult patients, aged between 40 and 80 years, with colorectal cancer requiring a segmental colectomy were randomized to receive open surgery or laparoscopic surgery and standard care or fast-track care by protocol in a separate enhanced recovery environment. Patients and nursing staff were blinded to the type of surgical intervention by the use of abdominal bandages to obscure the incision(s). There were defined discharge criteria for all groups.

The primary endpoint was hospital stay. The secondary endpoints were quality of life at 2 and 4 months postoperatively, measured using the Short Form Health Survey (SF-36) and Gastrointestinal Quality of Life Index (GIQLI) forms. Also cost, morbidity, 30-day mortality, patient satisfaction, and readmission rates were recorded. Analysis was on an intention to treat basis.

The results revealed that for the primary endpoint of postoperative hospital stay:

- Patients receiving laparoscopic surgery and fast-track care, the post-op stay was 5 (4–7) days
- Patients receiving laparoscopic surgery and standard care, the post-op stay was 6 (4–8.5) days
- Patients receiving open surgery and fast-track care, the post-op stay was 6 (4.5–10) days
- Patients receiving open surgery and standard care, the post-op stay was 7 (6–10.5) days

There was no difference in any of the secondary outcomes. Regression analysis showed that only laparoscopic surgery was an independently predictive factor for improved outcome by these criteria.

The conclusion of the authors was that the optimal intervention of segmental colectomy for cancer was a combination of laparoscopy and a fast-track protocol. In the event of open surgery being necessary, this was best carried out in a fast-track environment.

EnROL: A Multicenter Randomized Trial of Conventional Versus Laparoscopic Surgery for Colorectal Cancer Within an Enhanced Recovery Program

This was a phase III multicenter randomized controlled trial of colorectal cancer resection with adult patients randomized between open and laparoscopic surgery, all of whom were managed within an enhanced recovery pathway. Of the 202 patients recruited at 12 UK hospitals, all had significant experience in colorectal laparoscopy (>100 colectomies and >50 total mesorectal resections). The nature of the surgery was blinded to the patient and the caregivers in the same way as the LAFA trial. The primary outcome is physical fatigue as measured by the physical component of the Multidimensional Fatigue Inventory (MFI-20). Secondary endpoints include length of stay, complications, readmissions, reoperations, quality of life, cosmesis, costs, and other components of the MFI-20.

Analysis shows that total hospital stay was reduced from 7 to 5 days for colonic resection and from 8 to 5 days for rectal resection when managed laparoscopically within an enhanced recovery pathway. The conclusion is that laparoscopy is an additional advantage to recovery for patients with colorectal cancer managed within ERAS.

Almost all the published work looking at this subject deals with colorectal resection, where enhanced recovery is most developed and where there has been a rapid expansion in laparoscopic approach. Some other areas of surgery have also been subject to investigation, for example, the previously described Dutch study (ORANGE II) looking at outcomes following laparoscopic versus open left lateral liver resection within an ERAS whose primary endpoint is functional recovery.

For laparoscopic sleeve gastrectomy, a randomized controlled trial of ERAS versus open surgery, which included an additional comparison with historical controls, showed a 1-day stay for laparoscopy versus 2-day stay for standard care and a 3-day stay for historical controls [47]. The reduction in hospital stay for the enhanced recovery group was statistically significant, and there was no increase in morbidity.

Nonrandomized evidence in other areas of surgery include comparisons of outcomes against matched historical controls for ileocecal resection, which confirms a reduction of hospital stay by integrating ERAS into the laparoscopic management of Crohn's disease [48]. A large study of colorectal resection ($n = 806$) comparing outcomes of open and laparoscopic resection, all managed within ERAS, revealed 3.9 days versus 8.4 days in favor of the laparoscopic group [49].

Clearly this nonrandomized data has inherent bias that needs to be taken into account when analyzing the literature.

To date, ERAS guidelines for colon, rectum, liver, gynecology, bariatric, and pancreatic surgery have been published. Evidence of significant benefit of an ERAS program have been demonstrated in liver, pancreas, bariatric, colon, and rectal surgery [50–54]. Both the ERAS program and laparoscopic surgery aim to reduce complications and improve the quality and rapidity of recovery after surgery. An important synergistic value of both laparoscopy and ERAS applied together was published in 2012, suggesting that laparoscopy should be integrated into an ERAS program whenever possible.

Physiological Consequences of Minimally Invasive Surgery

The stress response in surgery is directly proportional to the insult of cellular injury. Cellular injury can occur in various ways such as the abdominal wall incision, handling of the bowel, retraction, thermal injury, and dissection. The duration of the inflammatory response can be attenuated, however, by enhanced recovery and is certainly shortened by minimally invasive surgery [55]. C-reactive protein (CRP) is commonly used as a marker of surgical stress, but interleukin-1 and interleukin-6 have been shown to be a more useful, though a less readily available, measure [56]. Minimally invasive platforms such as robotic surgery and laparoscopic surgery allow for smaller incisions, less bowel handling, accurate dissection, and reduced blood loss. Blood loss has time and time again been proven to be significantly lower in laparoscopic surgery than open surgery, and evidence suggests robotic surgery may offer a minor additional benefit [24].

Blood is not simply red cells but also plasma and proteins; therefore, losing blood affects not only the cardiac output but also the acid base balance. In addition, metabolically healthy patients undergoing surgery develop net losses of nitrogen of 40–80 mg, equivalent to 1.2–2.4 kg of skeletal muscle. This loss of muscle is often sufficient for a diagnosis of sarcopenia, a pathological loss of skeletal muscle with physical detriment – another growing field of interest in predicting surgical and oncological outcomes [57]. Minimizing blood loss, and subsequently maintaining a more stable acid base balance, and losing less protein are some of the numerous benefits of minimally invasive surgery. Evidence tells us that although surgical approach has a key role in limiting the detrimental effects of surgery, via enhanced recovery with preoperative carbohydrate loading, good analgesia, and early postoperative feeding, the catabolic effects of surgery can be largely avoided even in open surgery [58].

Of course not all elements of minimally invasive surgery are desirable, namely, the effects of pneumoperitoneum and often a steep head-down position. Raised intra-abdominal pressures lead to reduction in preload and increase in aortic afterload. The degree of effect is governed by the fluid status of the patient and is therefore again minimized by adherence to enhanced recovery principles, such as avoiding bowel preparation and prolonged starvation. A prolonged period of head-down position can lead to cerebral edema and airway edema, making extubation more difficult. Longer procedures with large volumes of carbon dioxide insufflated through the abdominal cavity can lead to an acidosis.

One final key benefit of minimally invasive surgery is the potential to reduce gastrointestinal ileus. As previously stated, inflammation is reduced with a minimally invasive approach. All inflammation leads to increased bowel permeability, and reduced inflammation combined with fluid optimization leads to earlier return of GI function in almost all studies that document this outcome.

Conclusion

The focus on the different minimally invasive approaches is on improving the cancer-related outcomes, reducing the morbidity of pelvic surgery, and reducing conversion rates. However, all have a similar capacity to reduce the trauma and immunological impact of surgery compared to an open approach. Minimally invasive surgery is both an important enabling technology for many of the elements of ERAS and an independent predictor of good outcome [42]. It independently has the capacity to reduce complications, which is the ultimate goal of an ERAS program. MIS enables reduced pain and opiate requirement, early mobilization, less impact on fluid shifts, and reduced ileus.

A minimally invasive approach to surgery has clear advantages for improved and more rapid recovery, reduced general complications, and reduced wound-related complications including incisional hernia and fewer adhesions. It is also an enabler for successful administration of many of the major components of ERAS, such as opiate-sparing analgesia and optimized fluid therapy.

Historically, as was the case with laparoscopy and now with robotic and transanal surgery, we are on the learning

curve for implementation, with no substantial evidence for one technology over another. We may well be in a transition where new evidence is about to reshape the landscape for what is considered the best minimally invasive approach, but it does not appear to be the case that laparoscopy can be proven inferior to any of the new technologies with the confidence that is necessary. As further data emerges, it is likely that a tailored rather than blanket approach will be applied for patients most suited to each technology, with a difficult balance of patient wishes against oncological outcomes. Qualitative data is ever increasing and will be vital in the decision-making consultation.

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Tubes and Drains: Current Updates on Evidence on Their Role Within Recovery

20

Gloria Salvo and Pedro T. Ramirez

Introduction

The principles of enhanced recovery after surgery (ERAS) programs are based on the implementation of a number of guidelines in the perioperative period in order to improve the overall physical and functional recovery of patients. Compliance with such implementation has been shown to improve such outcomes. In an effort to establish ERAS programs, groups should develop strategies within their multidisciplinary team in order to be certain that all parameters in the ERAS guidelines are applied [1, 2].

Current ERAS guidelines emphasize the importance of avoiding routine nasogastric intubation and further suggest that nasogastric tubes inserted during surgery should be removed before reversal of anesthesia. In addition, the same guidelines strongly recommend that peritoneal drainage not be recommended routinely including in patients undergoing bowel surgery or lymphadenectomy, as in the setting of cancer surgery.

In this chapter, we provide a detailed analysis of the evidence thus far published in the literature on the utility and indications of nasogastric tubes and peritoneal drains with an emphasis on the supportive evidence for the discontinuation of the routine use of such tubes and drains. Our aim is to demonstrate that there is no current indication for the routine use of tubes or drains in the setting of an ERAS program.

Nasogastric Tubes

Nasogastric decompression was routinely used for many years for the purposes of evacuating gas and liquid from the stomach for therapeutic, as in patients with distention and vomiting, or for diagnostic purposes, as in the case of gastrointestinal bleeding (Fig. 20.1). At the turn of the twentieth century, it became increasingly used in most major abdominal surgeries in order to prevent the consequences of postoperative ileus. Levin initially introduced this principle in 1921, [3] and its use was then popularized by Wangensteen and Paine [4] during the 1930s in the treatment of acute intestinal obstruction and postoperative ileus. The proposed rationale in the use of nasogastric intubation is that it decreases nausea, vomiting, and gastric distension after surgery. Others have also proposed that it decreases wound and respiratory complications, such as pulmonary aspiration and pneumonia, and that it also reduces the incidence of anastomotic leaks after gastrointestinal surgery [5]. However, this practice has been increasingly challenged over the last several years, and, in fact, many have proposed that routine use of nasogastric tubes is no longer warranted.

A previously published Cochrane Review by Verma and Nelson [6] investigated the efficacy of routine nasogastric decompression after abdominal surgery. In this study, the investigators included patients having abdominal surgery of any type—emergency or elective—who were randomized prior to the completion of the operation to receive a nasogastric tube and keep it in place until intestinal function had returned versus those receiving either no tube or early tube removal in surgery, in recovery, or within 24 hours of surgery. The investigators excluded patients who underwent laparoscopic abdominal surgery and patient groups having gastric decompression through gastrostomy. The authors included a total of 37 studies that met eligibility criteria encompassing 5711 patients: 2866 randomized to routine tube use and 2845 randomized to selective or no tube use. Patients not having routine tube use had an earlier return of bowel function ($p < 0.00001$), a decrease in pulmonary complications ($p = 0.09$), and an insignificant trend toward increase in risk of wound infection ($p = 0.39$) and ventral hernia (0.09). Interestingly, the rate of anastomotic leaks was no different between groups ($p = 0.70$). The investigators noted that vomiting seemed to favor the routine use of nasogastric tube but at the expense of increased patient discomfort.

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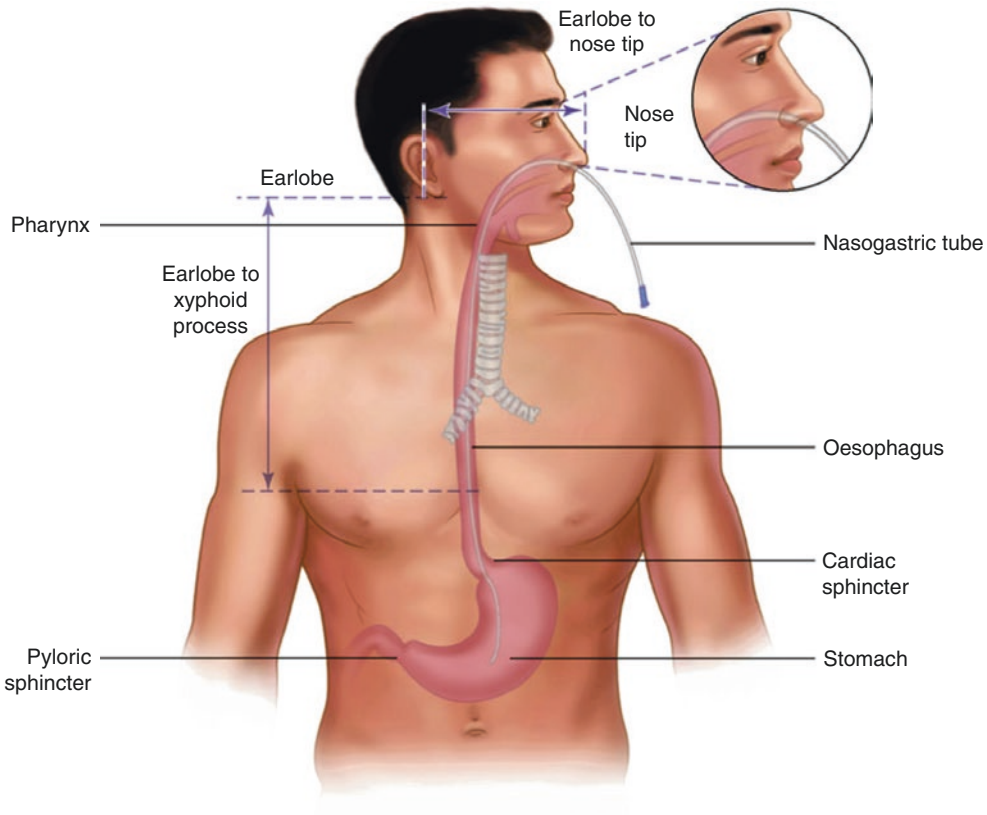

Fig. 20.1 Nasogastric tube placement. (Reprinted with permission from Nguyen et al. [30])

The length of hospital stay was shorter when no tube was used and no adverse events specifically related to the tube insertion (direct tube trauma) were reported in that study. In their conclusion, the authors remarked that routine nasogastric decompression does not accomplish any of its intended goals and should be abandoned.

This review drew some very important conclusions as it pertains to each of the proposed benefits of nasogastric intubation, and the following section will highlight some of these findings with a particular emphasis of time to flatus, pulmonary complications, wound infection, anastomotic leak, incisional hernia, length of stay, and adverse events:

- *Time to flatus* – There was no benefit to nasogastric suction in hastening return of gastrointestinal function as measured by time to flatus. In fact, the authors described that there was an opposite effect with significant benefit when no tube was used. In evaluating only patients having colon surgery, an earlier return of bowel function was seen in patients who had no tubes placed. Similarly, there was no benefit of nasogastric tube placement in patients having gastric resection [6].
- *Pulmonary complications* – In a subgroup analysis of studies evaluating patients who underwent colon surgery, there was no difference in pulmonary complications when comparing patients who had nasogastric tube placement versus those who did not. In addition, among individuals who had upper gastrointestinal surgery, the risk of pulmonary complications was lower in patients who did not have nasogastric tube placement [6].
- *Wound infections* – Routine use of nasogastric decompression did not impact the rate of wound infection, and this included patients who only had upper gastrointestinal surgery [6].
- *Anastomotic leak* – The rate of anastomotic leak was no different among patients with or without nasogastric drainage. This included patients who only had colon surgery [6].
- *Incisional hernia* – Although the number of studies is limited in evaluating this outcome, there is no evidence that placement of nasogastric drainage impacts the rate of ventral incisional hernias [6].
- *Length of hospitalization* – The majority of studies in this meta-analysis showed that patients who did not undergo placement of nasogastric drainage usually had a shorter length of hospital stay [6].
- *Adverse events* – The rate of adverse events from nasogastric tube placement remains very low, although events such as intracranial insertion and esophageal perforations have been reported [6].

When considering the subject of nasogastric drainage, many would question whether in certain circumstances this practice may provide a benefit given unique surgical scenarios

or disease sites. The goal of this next section of the chapter is to specifically address the published data pertaining to what most would consider the most pertinent circumstances.

Esophageal Surgery

The routine use of nasogastric tubes has been abolished in most types of gastrointestinal surgery after the introduction of ERAS programs. A study by Giacopuzzi et al. [7] evaluated the feasibility of ERAS for esophagectomy. In that study, the authors showed that there was an improvement in the ERAS group in terms of earlier extubation, earlier intensive care unit discharge ($p < 0.01$), earlier thoracic drain, urinary catheter ($p < 0.01$), nasogastric tube removal ($p = 0.02$), earlier mobilization ($p < 0.01$), and earlier resumption of oral feeding ($p < 0.01$). However, in the setting of esophagectomy, this remains a topic of debate. Esophagectomy is considered to be different from other types of upper gastrointestinal surgery because of the use of gastric conduit to restore gastrointestinal continuity. Therefore, the concern is that fluid accumulation and gastric distention might increase the risk of aspiration and anastomotic leaks when the gastric conduit is not routinely decompressed postoperatively.

Recently, Weijs et al. [8] performed a systematic review and meta-analysis to determine the effect of routine nasogastric decompression on anastomotic leakage, aspiration pneumonia, mortality, and recovery. In total, seven comparative studies were included, four randomized controlled trials and three retrospective trials. The authors found no difference in anastomotic leakage, pneumonia, or mortality between routine nasogastric decompression and early removal of the nasogastric tube after esophagectomy.

Data from a single-center, prospective randomized controlled trial evaluated the effect of conventional versus early nasogastric tube removal on postoperative complications after esophagectomy. A total of 80 patients took part in this study. In the conventional nasogastric tube removal group, the tube was removed on postoperative day 7, while in the experimental group, the tube was removed on postoperative day 1. The authors found that the incidence of postoperative major complications such as pneumonia, anastomotic leakage, recurrent nerve palsy, gastrointestinal bleeding, and nasogastric tube reinsertion rate was not different between the groups. Hence, showing that nasogastric tubes can be removed earlier than conventional methods.

Gastric Surgery

Postoperative nasogastric or nasojejunal decompression after gastrectomy for gastric cancer has been used extensively in the past. The proximal anastomoses (esophagojejunal, gastrojejunal, or gastroduodenal) and the duodenal stump pose a possible risk for early postoperative fistula formation. In addition, radical gastrectomies with lymph node dissection performed for gastric cancers may impact gut motility after surgery. Therefore, the rationale for placement of nasogastric or nasojejunal intubation is based on the potential decrease in postoperative ileus, gastric distension, or leakage from the duodenal stump. In a recent meta-analysis by Wang and colleagues [9], the authors evaluated the necessity of routine nasogastric decompression after radical gastrectomy for gastric cancer. In this review, the authors only included prospective randomized trials where outcome measures included time to first flatus, time to starting oral diet, anastomotic leakage, pulmonary complications, wound dehiscence, length of hospital stay, morbidity, and mortality. A total of 8 randomized controlled trials were included in the study totaling 1141 patients: 570 patients receiving nasogastric or nasojejunal decompression and 571 patients who did not. When stratified by the type of gastrectomy or gastrojejunostomy, no significant differences were noted in anastomotic leakage, pulmonary complications, wound dehiscence, morbidity, and mortality. The authors did find that the group without nasogastric tube placement had a shorter time to oral diet ($p < 0.001$) and a marginally shorter end of hospital stay ($p = 0.05$). Also, the group without nasogastric drainage had significantly shorter time to first flatus ($p = 0.001$), especially with Roux-en-Y reconstruction ($p = 0.0002$). In this study, the authors concluded that routine nasogastric decompression appears to be unnecessary after gastrectomy for gastric cancer, irrespective of the extent of resection, and the type of digestive reconstruction.

Liver Surgery

The value of routine nasogastric decompression after elective hepatectomy remains a topic of debate. Pulmonary complications are common after hepatic surgery and thus the interest in this particular surgery lies in whether nasogastric decompression could reduce the risk of such complications. In a recent study by Ichida et al. [10], the investigators studied 210 consecutive patients undergoing hepatectomy who were randomized either receive nasogastric tube draining ($N = 108$) or none ($N = 102$). In those receiving a nasogastric tube, the drain was left in place after surgery until the patient passed flatus or stool. The investigators found that there was no difference between the groups in terms of overall morbidity (34.3 vs. 35.3%; $p = 0.99$), incidence of pulmonary complications (18.5 vs. 19.5%, $p = 0.84$), frequency of postoperative vomiting (6.5 vs. 7.8%, $p = 0.70$), time to start of oral intake (3 vs. 3days, $p = 0.69$), or postoperative hospital stay (19 vs. 18 days,

$p = 0.37$). The authors concluded that nasogastric decompression after elective hepatectomy does not appear to have any advantages.

Colon and Rectal Surgery

The routine use of nasogastric drainage after elective colon and rectum surgery has been advocated as a way to decrease air and fluid accumulation and decompress the gastrointestinal tract in order to prevent abdominal distension, nausea, and vomiting and to promote the recovery of gastrointestinal function and decrease hospital stay. In a prior meta-analysis totaling 1416 patients, the authors noted that although patients with nasogastric tube placement had less vomiting ($p < 0.00001$), they did experience higher rates of pharyngolaryngitis ($p < 0.00001$) and more respiratory infections ($p = 0.004$). They noted no statistically significant differences in nausea, wound infection, or intestinal obstruction. Thus concluding that nasogastric tube drainage should not routinely be recommended after elective colon or rectum surgery [11].

Abdominal Drains

Surgeons have historically advocated the use of abdominal drains for three primary reasons: first, to allow continuous drainage from an abscess, until complete obliteration of the cavity; second, to provide a path of least resistance to the exterior of the abdominal cavity, as in the case of directing the course of a potential fistula with the goal of sealing it from the general peritoneal cavity; and third, to evacuate blood and serum. There are a number of drains that are currently used in the abdominal cavity and these include, but are not limited to, simple conduit (Penrose drain, corrugated drains, and simple tube drains), suction drains, or sump drains (double-lumen systems) [12]. The next section of the chapter will focus on specific surgeries of the abdominal cavity and address the literature pertaining to such procedures and outcomes of routine use of abdominal drainage in such settings.

Pancreatic Surgery

Pancreatic surgery is commonly performed to treat a number of pancreatic and extra-pancreatic diseases, including pancreatic cancers, chronic pancreatitis, and biliary and duodenal malignancies. The current mortality rates are low, often referenced as less than 5%; however, overall morbidity remains high, ranging from 30% to 60% [13]. The most common complications documented after pancreatic surgery include delayed gastric emptying (19–23%), pancreatic fistulae (2–30%), intra-abdominal abscess (9–10%), wound infections (5–15%), and postoperative bleeding (1–8%) [14, 15]. In an effort to reduce postoperative complications after pancreatic resections, prophylactic drains have been traditionally placed in order to avoid accumulation of bile, pancreatic juice, or blood, which might require additional procedures. There are a number of reasons for placement of abdominal drains after pancreatic resections, and these include (1) drainage of established intra-abdominal collections (bile, pancreatic juice, or pus); (2) prevention of further fluid accumulation; and (3) identification and monitoring of any fistula or bleeding [16]. Recently, there has been increasing debate regarding the efficacy of routine abdominal drains after pancreatic surgery. Many surgeons argue that abdominal drains may fail to reduce postoperative complications because a drain may become sealed off and ineffective within a few days after pancreatic surgery. In addition, one might argue that the drain itself may act as a foreign body, and may interfere with wound healing and the drainage tube also potentially creates a pathway for contamination, thus increasing the risk of postoperative infectious complications. Even more concerning, abdominal drainage after pancreatic surgery may be associated with rare complications, such as bowel perforation, hernia, and bleeding.

In a recent Cochrane systematic review, Zhang and colleagues [17] assessed the benefits and harms of routine abdominal drainage after pancreatic surgery, compared the effects of different types of surgical drains, and evaluated the optimal time for drain removal. They included all randomized controlled trials that compared abdominal drainage versus no drainage in patients undergoing pancreatic surgery. They also included randomized trials that compared different types of drains and different schedules for drain removal. The authors included 4 studies with 1110 participants, who were randomized to the drainage group ($N = 560$) and the no drainage group ($N = 550$) after pancreatic surgery. There was no difference in mortality at 30 days between groups (1.5% with drains versus 2.3% with no drains; risk ratio [RR] 0.78, 95% confidence interval [CI] 0.31 to 1.99). The rate of intra-abdominal infection was similar between the groups (7.9% versus 8.2%; RR 0.97, 95% CI 0.52 to 1.80), or additional radiological interventions for postoperative complications (10.9% versus 12.1%; RR 0.87, 95% CI 0.79 to 2.23). The rate of wound infection was also very similar between the groups (9.8% versus 9.9%; RR 0.98, 95% CI 0.68 to 1.41). There was no difference in morbidity (61.7% versus 59.7%; RR 1.03, 95% CI 0.94 to 1.13) or length of hospital stay (MD −0.66 days, 95% CI −1.60 to 0.29) between groups. Health-related quality of life was measured with the pancreas-specific quality-of-life questionnaire (Functional Assessment of Cancer Therapy–Pancreatic Cancer [FACT-PA]), a scale of 0–144 with higher values indicating a better quality of life.

Drain use led to similar quality of life scores, measured at 30 days after pancreatic surgery, when compared with no drain use (105 points versus 104 points). When considering the types of drains used, the authors included one trial involving 160 participants, who were randomized to the active drain group ($N = 82$) and the passive drain group ($N = 78$) after pancreatic surgery. An active drain led to similar mortality at 30 days (1.2% with active drain versus 0% with passive drain) and morbidity (22.0% versus 32.1%; RR 0.68, 95% CI 0.41 to 1.15), when compared with a passive drain. Lastly, in evaluating the timing of drain removal, the authors included one trial involving 114 participants, who were randomized to the early drain removal ($N = 57$) and the late drain removal ($N = 57$) after pancreatic surgery. There was no mortality in either group. Early drain removal was shown to slightly reduce morbidity (38.6% with early drain removal versus 61.4% with late drain removal; RR 0.63, 95% CI 0.43 to 0.93), length of hospital stay (MD −2.10 days, 95% CI −4.17 to −0.03; 21.5% decrease of an "average" length of hospital stay), and hospital costs (MD −EUR 2069.00, 95% CI −3872.26 to −265.74; 17.0% decrease of "average" hospital costs). The authors concluded that it was unclear as to whether routine abdominal drainage has any impact on the reduction of mortality at 30 days or on postoperative complications after pancreatic surgery.

Gallbladder Surgery

Cholecystectomy is currently considered the best treatment option for patients with symptomatic gallstones. Drains have been used after this procedure on a routine basis for the purpose of detecting early bile/blood leak and to allow the CO^2 insufflation used during laparoscopy to escape in order to decrease shoulder pain and postoperative nausea and vomiting.

A recent study evaluated the benefits or potential harms of routine abdominal drainage in uncomplicated laparoscopic cholecystectomy [18]. A total of 1831 participants were randomized to drain (915 participants) versus "no drain" (916 participants) in 12 trials. Nine trials included patients undergoing elective laparoscopic cholecystectomy exclusively. The average age of participants in the trials ranged between 48 years and 63 years. There was no significant difference between the drain group (1/840) (adjusted proportion: 0.1%) and the "no drain" group (2/841) (0.2%) (RR 0.41; 95% CI 0.04 to 4.37) in short-term mortality. There was no significant difference between the drain group (7/567) (adjusted proportion: 1.1%) and the "no drain" group (3/576) (0.5%) in the proportion of patients who developed serious adverse events (RR 2.12; 95% CI 0.67 to 7.40) or in the number of serious adverse events in each group: drain group (12/646) (adjusted rate: 1.5 events per 100 participants) versus "no drain" group (6/640) (0.9 events per 100 participants; rate ratio 1.60; 95% CI 0.66 to 3.87). There was no significant difference in the quality of life between the two groups (one trial; 93 participants; SMD 0.22; 95% CI −0.19 to 0.63). The proportion of patients who were discharged as day-procedure laparoscopic cholecystectomy seemed significantly lower in the drain group than the "no drain" group (one trial; 68 participants; drain group 0/33 [adjusted proportion: 0.2%] versus "no drain" group 11/35 [31.4%]; RR 0.05; 95% CI 0.00 to 0.75). There was no significant difference in the length of hospital stay between the 2 groups (5 trials; 449 participants; MD 0.22 days; 95% CI −0.06 days to 0.51 days). There was no significant difference in the return to normal activity and return to work between the groups in one trial involving 100 participants. The authors concluded that there is no evidence to support the routine use of drain after uncomplicated laparoscopic cholecystectomy.

Bariatric Surgery

Gastrointestinal leaks remain one of the primary concerns after bariatric surgery, resulting in substantial morbidity for patients. Several studies have reported on the incidence of gastrointestinal leak after gastric bypass and sleeve gastrectomy to be as high as 5.6% and 2.4%, respectively [19, 20]. Given the fact that mortality after leak has been reported to be up to 17%, with leaks at the jejunojejunostomy being the most morbid, surgeons continue to strive to find solutions in order to decrease the rate of this complication [21].

Given the paucity of data on the subject of routine drainage after bariatric surgery, Doumouras and colleagues [22] compiled information from all hospitals in the United States that participated in the 2015 Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program. Only patients undergoing sleeve gastrectomy or gastric bypass were included in the analysis. The main outcomes of interest were anastomotic leak, reoperation, all-cause mortality, readmission, and mortality. A total of 142,631 patients were included in the analysis. The authors found that after adjusting for major clinical variables, the odds of anastomotic leaks increased by 30% with the placement of a drain (odds ratio [OR]: 1.30, 95% CI: 1.067–1.57, $P = 0.01$) while the odds of reoperation increased by 17% (95% CI: 1.06–1.30; $P = 0.01$). The odds of all-cause morbidity increased 19% (95% CI: 1.14–1.25, $P < 0.01$), and odds of readmission were significantly higher (OR: 1.12, 95% CI: 1.06–1–19, $P < 0.01$). The odds of mortality did not change significantly with the placement of a drain. The study provided no evidence that routine drainage is beneficial to patients undergoing bariatric surgery, and that, in fact, it may be associated with an increase in major morbidity and thus the use of drainage should be restricted to only very select, high-risk patients.

Colorectal Surgery

The use of drains after colorectal surgery has been a subject of debate for several decades. In 2004, the Cochrane Collaboration performed a review of the literature on prophylactic use of drains in colorectal surgery [23]. A total of 1140 patients from 6 randomized studies were included comparing drains vs. no drains after anastomosis in elective colorectal surgery. The primary objective was to determine impact of drains on clinical anastomotic leakage. The study showed an overall mortality of 3% in the patients who had drains compared with 4% in those without drains. In addition, the study showed that extra-abdominal complications were noted in 7% in the drainage group compared to 6% for the non-drainage group.

One might argue that prophylactic drainage may offer a benefit in the setting of low pelvic anastomosis. After a mesorectal resection, raw surfaces may secrete serous or hemorrhagic fluid into the dependent cavity of the pelvis. In a study by Yeh et al. [24], the authors prospectively evaluated 978 patients who underwent a low anterior resection with the objective of determining if prophylactic pelvic drainage impacted rates of anastomotic leak. Their results showed that the clinical anastomotic leak rate was 2.8% and that routine use of pelvic drainage was not justified and should be discouraged.

Gynecologic Surgery

Pelvic and/or Para-aortic Lymphadenectomy

Pelvic and/or para-aortic lymphadenectomy continues to be performed in certain settings in the surgical management of patients with gynecologic malignancies. However, the procedure may be associated with a significant risk of lymphocyst formation in the retroperitoneal space. Although frequently asymptomatic, lymphocysts can lead to leg edema, ureteral obstruction, pelvic pain, deep vein thrombosis, ileus, secondary infection, and fistula. Peritoneal drainage of the operative field had been advocated for many years in the field of gynecologic oncology as a strategy to prevent lymphocyst formation and febrile morbidity; however, as there was an increase in the tendency to leave the peritoneum open and allow for transperitoneal resorption of lymph fluid throughout the abdominal cavity, this policy has been challenged, and routine drainage is no longer considered a standard of care.

The European Organization for Research and Treatment of Cancer-Gynecological Cancer Group (EORTC-GCG) performed a prospective multicenter randomized trial in Europe to compare the incidence of lymphocyst formation and postoperative morbidity between two groups of patients who underwent radical hysterectomy and pelvic lymph node dissection [25]. Patients were randomized to either pelvic drainage or no drainage. The pelvic peritoneum was left open in all patients and the vaginal cuff was closed. In the drainage arm, 2 passive or active suction drains were placed in the retroperitoneal fossa and inserted via the vagina or the abdominal route, according to institutional policy. Drains were removed when fluid loss was less than 50 mL in 24 hours. At 1 and 12 months postoperatively, imaging was performed by ultrasound or computed tomography (CT) scan. A total of 234 patients were randomized with a median follow-up of 13.3 months. Altogether, lymphocysts were found in 30.8% of patients in the drains group and in 37.6% of patients in the no-drains group. Symptomatic lymphocysts were seen in 5.9% of patients in the drains group versus 0.9% in the no-drains group ($p = 0.06$). The presence of metastatic nodes was not related to the incidence of lymphocysts, and neither was the number of lymph nodes removed. The authors concluded that drains might be safely omitted after radical hysterectomy and pelvic node dissection.

In a recent Cochrane systematic review by Charoenkwan et al. [26], the authors assessed the effects of retroperitoneal drainage versus no drainage after pelvic lymphadenectomy on lymphocyst formation and related morbidities in women with gynecologic cancer. The review included 4 studies with 571 women. Regarding short-term outcomes (within 4 weeks after surgery), retroperitoneal drainage was associated with a comparable rate of overall lymphocyst formation when all methods of pelvic peritoneum management were considered together (2 studies; 204 women; RR 0.76, 95% CI 0.04 to 13.35; moderate-quality evidence). When the pelvic peritoneum was left open, the rates of overall lymphocyst formation (1 study; 110 women; RR 2.29, 95% CI 1.38 to 3.79) and symptomatic lymphocyst formation (2 studies; 237 women; RR 3.25, 95% CI 1.26 to 8.37) were higher in the drained group. At 12 months after surgery, the rates of overall lymphocyst formation were comparable between the groups (1 study; 232 women; RR 1.48, 95% CI 0.89 to 2.45; high-quality evidence). However, there was a trend toward increased risk of symptomatic lymphocyst formation in the group with drains (1 study; 232 women; RR 7.12, 95% CI 0.89 to 56.97; low-quality evidence). Based on these findings, the authors concluded that placement of retroperitoneal tube drains has no benefit in the prevention of lymphocyst formation after pelvic lymphadenectomy in women with gynecological malignancies. When the pelvic peritoneum is left open, the tube drain placement is associated with a higher risk of short- and long-term symptomatic lymphocyst formation.

Bowel Resection for Tumor Cytoreduction

Another potential scenario in gynecologic oncology where the routine placement of abdominal drains has been questioned is after large bowel resection in the setting of tumor

reductive surgery for advanced ovarian cancer. In a study published by Kalogera et al. [27], the authors retrospectively evaluated whether placement of suction drains decreased morbidity following anastomotic leaks. A total of 43 patients met inclusion criteria. The authors found no convincing evidence that routine prolonged pelvic drainage after large bowel resection yielded better outcomes in terms of shorter length of stay, earlier time to chemotherapy, or type of intervention required for management of anastomotic leak.

Groin Lymphadenectomy

The standard treatment for patients with early stage vulvar cancer consists of wide local excision of the tumor with a sentinel lymph node dissection. However, in certain settings, surgeons are still performing a complete inguinofemoral lymphadenectomy. Unfortunately, a complete lymphadenectomy has significant short- and long-term complications such as wound breakdown, wound infection, and formation of lymphoceles. In addition, for a number of patients, long-term complications such as lymphedema and cellulitis/erysipelas may significantly impact quality of life.

Many surgeons elect to drain the groin in order to prevent lymphocyst formation despite a lack of evidence to support this practice. In a recent study by Pontre et al. [28], the authors retrospectively investigated whether groin drains after inguinofemoral lymphadenectomy were associated with reduced postoperative morbidity in women undergoing surgery for vulvar cancer. A total of 71 patients were included, and inguinal drains were used in 67% of these patients, while the rest did not have their wounds drained. The most common postoperative complications recorded were wound infection (59.2%), groin lymphocyst (32.4%), and cellulitis (25.4%). Compared with patients in whom inguinal drains were placed, those in the "no drain" group had a significantly lower incidence of postoperative groin cellulitis (8.7% vs. 25.4%; $P = 0.039$). No significant differences were observed between patients in the "drain" and "no drain" groups in lymphocyst formation, wound infection, return to the operating room, duration of hospital stay, readmission post-discharge, and lower-limb lymphedema. The authors concluded that in patients undergoing inguinofemoral dissection for primary vulvar cancer, postoperative cellulitis occurred less frequently in patients without an inguinal drain and that the incidence of other postoperative complications was no different whether or not a drain was used.

Cesarean Delivery

Cesarean section is the most common operation performed on women worldwide. In this operation, it is not uncommon that surgeons may opt to use a sub-rectus drain or a subcutaneous drain in order to remove blood and serous fluid, given that accumulation of these may cause postoperative pain by irritation of the peritoneal lining or lead to bacterial infection. However, a drain may be ineffective if the blood clots, and patients may also find it uncomfortable and inconvenient. Many surgeons would argue that drains are not necessary because the peritoneum heals very rapidly and reabsorbs blood in this process; therefore, this issue has been a topic of debate among many.

To this end, Gates and Anderson [29] compared the effects of using a wound drain with not using such a drain at the time of Cesarean delivery. In addition, in this Cochrane Review, the authors evaluated the impact of different types of drains on maternal health and healthcare resources. The authors included 10 trials that recruited a total of 5248 women and found no evidence of a difference in the risk of wound infection, other wound complications, febrile morbidity, or pain in those who had wound drains compared with those who did not. The study concluded that the routine use of wound drains at the time of Cesarean section does not confer any substantial benefit to the patient.

Conclusion

In this chapter, we have reviewed the literature on the role of nasogastric tube decompression after abdominal surgery and the role of routine drainage of the abdominal cavity after numerable abdominal and pelvic surgeries. The results are very convincing by demonstrating that routine use of either nasogastric tubes or abdominal drains was not associated with a decrease in postoperative nausea or vomiting, time to return of normal bowel function, pulmonary complications, length of hospital stay, wound infection, anastomotic leak, lymphoceles, or lymphocysts. In fact, several studies showed a higher rate of postoperative complications and perioperative morbidity, including a decrease in patient satisfaction and quality of life.

To this end, routine use of nasogastric drainage or abdominal drainage should be avoided when implementing an ERAS program. In addition, efforts should be made to assure that all members of the team maintain a consistent and high level of compliance with this important item in the guidelines in order to achieve the greatest level of success reflected in patient outcomes.

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Part IV

Postoperative Management

Management of Postoperative Nausea and Vomiting (PONV)

21

Peter Kranke, Wolfram Wilhelm, and Leopold Eberhart

Introduction

In the recent years perioperative care has undergone major changes and improvements. On the one hand, pharmacological developments and improved technical interventions have been introduced to speed up recovery and render surgery less invasive. On the other hand, some interventions that had been applied for years have been critically questioned and assessed using the principles of evidence-based medicine. This has led to a stepwise reduction of preoperative and perioperative interventions, which means that patients are no longer exposed to unnecessary tubes, drains, excessive salt and fluid load, aggressive bowel preparation methods, and monitoring that impaired their homeostasis and may exert a negative influence on the recovery process. Apart from technical developments, effective pharmaceutical agents became available to minimize side effects in conjunction with anesthesia and thus facilitated the introduction of the enhanced recovery after surgery (ERAS) concept.

The current chapter is dedicated to the management of PONV. Emphasis is put on the principles of pharmacological prevention and treatment, a tailored approach to adjust the current available armamentarium to the individual patient, as well as the need for a multimodal approach in order to effectively decrease the occurrence of PONV in high-risk patients.

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Pharmacological Interventions to Facilitate Enhanced Recovery

The importance of pharmacological interventions in the context of ERAS perioperative care results from the fact that pharmacological agents play the major role in coping with undesirable effects of surgical procedures and anesthesia, such as pain and postoperative nausea and vomiting (PONV), which are important factors delaying the ambulation of patients and the transfer to the ward [1].

Although anesthesia can be safely administered also with older drugs, there is a growing awareness of the fact that newer drugs allow a more precise titration of anesthesia, thus leading to a more predictable anesthesia and a faster recovery, irrespective of the surgical procedure performed. For these reasons, newer and more expensive drugs have proved to be cost-efficient and favorably accomplish the existing armamentarium of available pharmacological agents. The trend in healthcare settings to apply activity-based pricing leads to that fact that from an integrated approach costly drugs may be applied with less overall costs.

Importance of Effective Antiemetic Prevention and Therapy in Enhanced Recovery

During the last two decades there have been considerable achievements regarding the management of postoperative nausea and vomiting. PONV must no longer constitute a "big problem" in the perioperative setting, even if inhalational anesthesia is used for maintenance, which notably increases the risk for PONV [2]. Since PONV may lead to significant delay during recovery and may even account for unanticipated hospital admissions after scheduled ambulatory surgery [3], it needs to be addressed in every ERAS protocol. Otherwise convalescence might be impaired, time to oral intake is prolonged, and a timely postoperative ambulation might become impossible for the patient. In summary,

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recovery of the functions of daily living may be delayed. There is increasing evidence that even the most promising antiemetic drugs if used as single prevention reduce PONV no more than approximately 30 relative percent [4, 5]. In addition, PONV can occur in up to 80% of patients at risk [4]. Therefore, multimodal drug prevention of PONV is indicated, especially if an increased risk is present.

Although the available screening tools based on established risk factors in order to elucidate which patient is at risk for PONV are by no means perfect with respect to its accuracy, they may guide antiemetic use and help to customize an antiemetic protocol [6–8].

The action of drugs can be considered to be independent without relevant interaction between classes of drugs (main receptor target). A combination of molecules with established and comparable efficacy will therefore result in addition of effect. Apart from established interventions, such as the use of a total intravenous anesthesia with propofol instead of inhalational agents for the maintenance of anesthesia, and the omission of nitrous oxide, 5-HT3 receptor antagonists (e.g., ondansetron), dimenhydrinate, transdermal scopolamine (hyoscine) or butyrophenones (droperidol or haloperidol), as well as dexamethasone or Neurokinin(NK)-1 antagonists (e.g. aprepitant) and potentially newer drugs just about to enter the market (e.g., amisulpride) should be available as prophylactic intervention [38]. Since most of these interventions are not associated with relevant costs and are not associated with major adverse effects (some agents in fact show desirable side effects, e.g., dexamethasone that acts as a co-analgesic and positively affects patient's mood), in some settings fixed multimodal prevention seems to be advisable rather than a strictly tailored approach [7]. This led to the adoption of a fixed combination of antiemetics in addition to maintenance of anesthesia using propofol in some fast-track protocols. Overall, the major factor to dramatically decrease an institutional PONV incidence is to apply enough antiemetics to patients [9].

Basic Pathophysiology of Postoperative Nausea and Vomiting

Vomiting may be viewed as a protective reflex that removes incorporated toxins from the gastrointestinal tract. The actual vomiting act is preceded by paresis of the gastrointestinal tract in order to slow down the absorption of toxins contained therein. The accompanying nausea also prevents further food intake. A fierce, retrograde giant contraction from the end of the jejunum then conveys the intestinal and gastric contents orally. By relaxing the proximal sections of the stomach and simultaneously turning on the abdominal press, the contents of the stomach are finally expulsed outward.

This complex extraneous reflex is coordinated by brain sections between the nucleus tractus solitarius and the olive. This zone receives neuronal impulses mainly from vagal afferents of the gastrointestinal tract, from the equilibrium system (sense of balance), and the area postrema. Located at the bottom of the fourth ventricle in the lower part of the rhomboid fossa, this part of the brain is functionally located outside the blood-brain barrier and can fulfill the function of a chemoreceptor for circulating substances in the blood. The transmission of emetogenic impulses to the emesis control center involves a large number of different neurotransmitters. Dopamine (via D2 receptors), serotonin (via 5-HT3 receptors), histamine (mainly via H1 receptors), and acetylcholine (muscarinic ACh receptors) play an important role in these emetic pathways (Fig. 21.1) [10, 11].

The emesis control center is also modified by dampening neural influences. These are mediated by numerous other receptors (including GABA-B, 5-HT1A, ghrelin, and cannabinoid receptors, and some other receptors and receptor subtypes).

Even with this very basic view of neurophysiology, it becomes clear that in order to achieve a satisfactory reduction of PONV, there cannot be one "magic bullet" to cope with PONV. Rather a multimodal approach is required in order to leapfrog toward a PONV-free hospital [12, 13].

Risk Factors

In adult patients, the following PONV risk factors (Fig. 21.2) have a clinical meaningful impact on the occurrence of PONV [8, 12]:

- Patient-specific risk factors such as female gender, nonsmoking status, history of PONV or motion sickness, as well as younger age
- Risk factors in conjunction with the anesthetic procedure, such as the use of nitrous oxide or volatile inhaled anesthetics and postoperative opioid administration
- Surgical risk factors such as duration and type of surgery

Overall, the impact of the surgical procedure itself has been overestimated in the past. In fact, the patient- and anesthesia-related factors play a more important role [14]. However, clustering patients beyond the risk to be expected based on the patient population and patient-related risk factors yielded an increased risk associated with thyroid surgery or on patients undergoing strabismus surgery.

Basic Measures Against Postoperative Nausea and Vomiting

Based on these risk factors, an expert group recommends so-called basic measures for PONV prophylaxis, which are essentially based on the avoidance of avoidable risks, for example, avoiding nitrous oxide and volatile inhaled anesthetics, and using propofol for anesthesia induction and

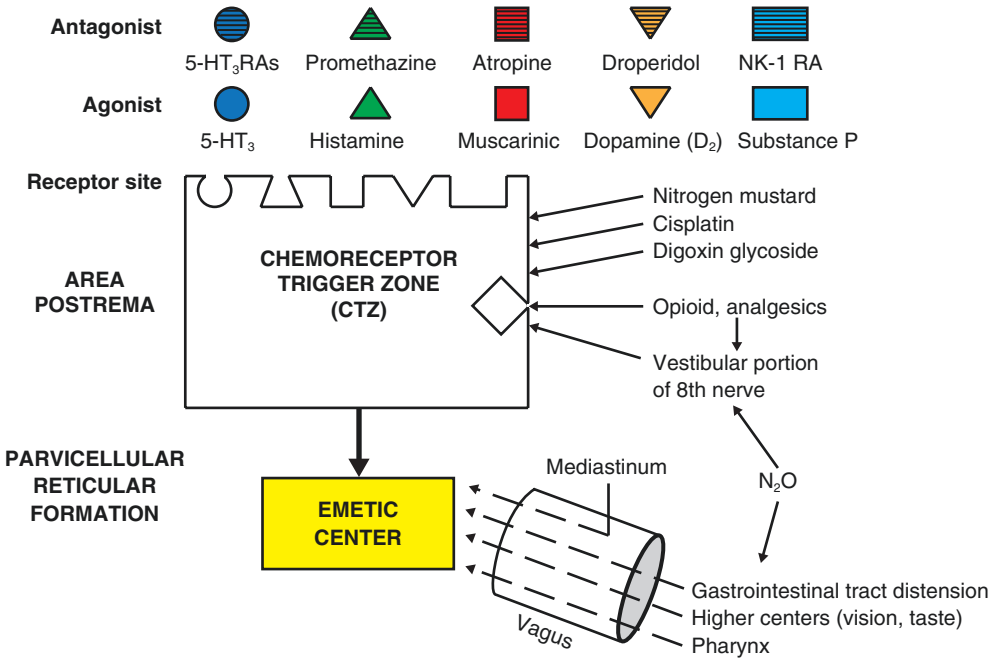

Fig. 21.1 The chemoreceptor trigger zone (CTZ) and emetic center. (Modified with permission from Watcha and White [10])

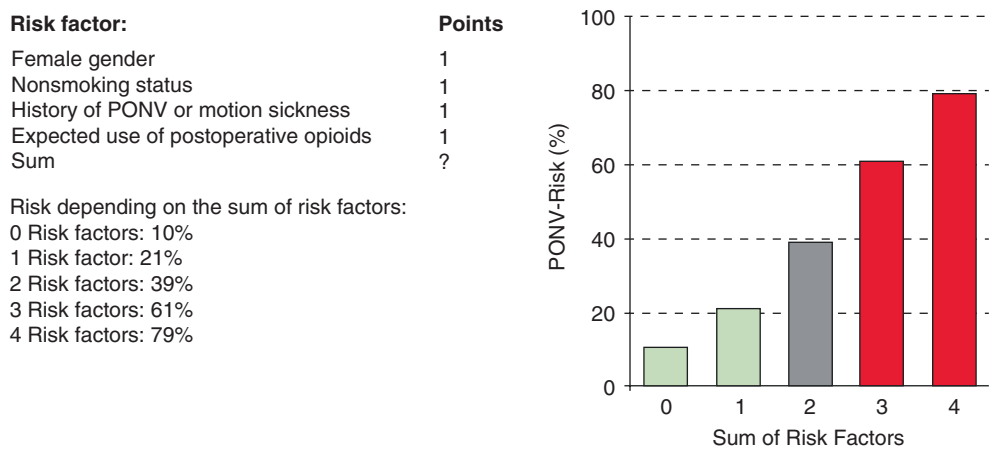

Fig. 21.2 Risk assessment using the number of major risk factors

maintenance, and performing small interventions in regional anesthesia instead of general anesthesia, thus limiting the need for postoperative opioid therapy. In this context, multimodal postoperative pain therapy using non-opioid analgesics and wound infiltration plays an important role, as there is a clear association between the postoperative opioid requirement and the PONV incidence [15]. In this respect, techniques of peripheral regional analgesia play an important role in the prevention of PONV.

Specific Measures of Postoperative Nausea and Vomiting Prophylaxis

For a specific pharmacological PONV prophylaxis, the following options are available and clinically well established (Fig. 21.3a, b):

Dexamethasone

The dexamethasone dose recommended for PONV is 4–8 mg and should ideally be given immediately after the anesthetic induction, as an antiemetic effect is expected to occur after 90 minutes at the earliest [16, 17]. Higher doses of glucocorticoids may lead to an increase in blood sugar levels postoperatively and impair glucose tolerance in the postoperative period. However, recent data showed that this is not a relevant clinical problem if relatively low dosages are used (e.g., 4 mg of dexamethasone). Nevertheless, it should be avoided to give repetitive doses over a series of days, e.g., due to the need for repetitive surgical procedures (wound revisions). Its use in patients with type 2 diabetes mellitus or metabolic syndrome is subject to a case-by-case decision. However, it must be kept in mind that so far no negative effect of single corticosteroid doses on wound healing could be found [18, 19].

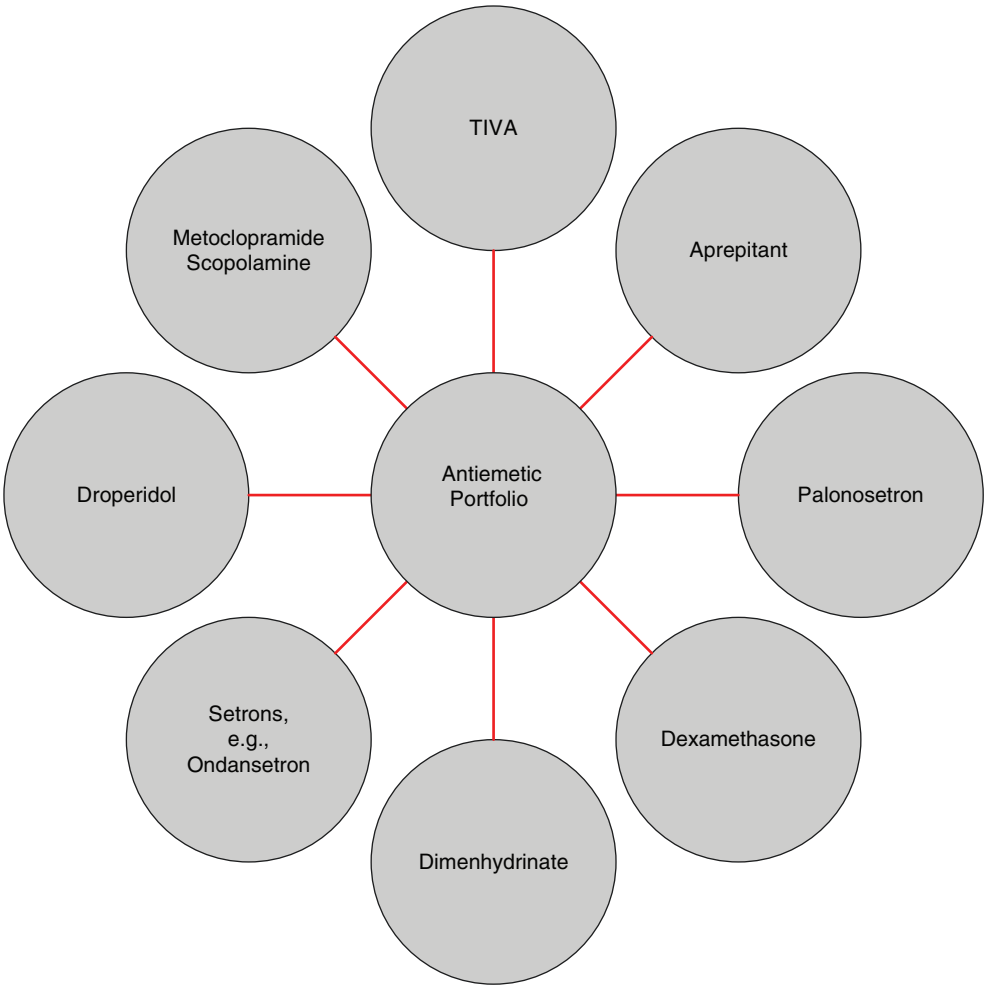

Fig. 21.3 (**a**) Portfolio of the armamentarium to cope with PONV

Several studies have provided clear evidence that there is no increased risk for wound infections or wound healing disorders in a single-dose perioperative administration [18, 20]. Also fears that corticosteroids could promote intraoperative spread of tumor cells could be refuted [21] so that dexamethasone (as well as other steroids) can also be used in oncological surgery—provided there is no increased risk of tumor lysis syndrome [22].

5-HT3 Receptor Antagonists

This substance group is also referred to as "setrons" and includes, e.g., ondansetron, granisetron, tropisetron, ramosetron, and palonosetron (the latter is not approved for PONV but is a drug with an extraordinary long half-life) [23, 24].

All setrons should be given just before the end of surgery. Only palonosetron can be applied at anesthesia induction due to its long duration of action of at least 36 hours. Setrons may prolong QT intervals. This is particularly important when using high doses for chemotherapy-induced nausea and vomiting (CINV), but seems less of a problem for the lower dosage required for the PONV indication. However, the effect should be known if these substances are combined with other QT-prolonging medications. The effectiveness of all setrons is largely comparable. Due to the longer duration of action, however, granisetron and palonosetron may exert a more pronounced effect in the late postoperative phase [25].

Neurokinin-1 Receptor Antagonists (NK-1-RA)

Neurokinin-1 receptor antagonists (NK-1-RA) include the substances aprepitant, casopitant, fosaprepitant, and rolapitant, of which currently only aprepitant is market-approved for PONV. This, however, is true only for the indication of CINV in conjunction with antineoplastic chemotherapies. Aprepitant is only available for oral application and can therefore be given in high-risk patients for PONV as part of premedication [26]. With fosaprepitant, a water-soluble prodrug is available that can be administered intravenously. This drug is used in some clinics (off-label) as a rescue antiemetic for patients in whom the conventional drugs have not sufficiently protected against the occurrence of PONV.

Butyrophenones

Butyrophenones include droperidol and haloperidol and other less-well-known drugs [27, 28]. Droperidol is used for PONV prophylaxis in a dosage of 0.625–1.25 mg intravenous (IV). It should be administered about 30 minutes before the end of surgery and is equally effective as the 5-HT3 antagonists. Droperidol also extends the QT interval, with the usual low dosage for PONV being even less dangerous than the QT prolongation of ondansetron. The combination of droperidol and ondansetron does not further increase QT time compared to single drug use. Alternatively, haloperidol can also be used in PONV (off-label), in a dose range of 0.5–1 mg. To minimize potential side effects, such as QT prolongation or extrapyramidal symptoms, it is usually recommended not to exceed a dose of 1 mg. However, haloperidol is not approved for this indication and therefore should not be used for primary prophylaxis. Amisulpride is a drug currently about to enter the market. It acts on dopamine 2/dopamine 3 (D2/D3) receptors and so far has not been associated with QT-prolongation and adverse neurological side effects based on the investigations published so far [29, 30]. Parkinson's disease represents an absolute contraindication for all dopamine antagonists.

Metoclopramide

Metoclopramide (MCP) is a weaker central dopamine-2 receptor antagonist with minimal effects on the 5-HT3 receptor. It accelerates gastric emptying and small intestinal passage. In a meta-analysis it could be shown that 10 mg MCP has only a limited effect on PONV; for higher dosages such as 25 and 50 mg, however, a meaningful effect could be detected [31, 32]. However, some regulaory entities recommend single doses not to exceed 10 mg and daily doses not to exceed 30 mg in adults. Following metoclopramide administration, as with the potent butyrophenones, extrapyramidal motor symptoms may occur. In addition, rapid IV administration may lead to lower blood pressure. Therefore, higher doses should best be administered via an infusion. Finally, MCP inhibits pseudocholinesterase, thus prolonging the action of succinylcholine and mivacurium. As already stated for the more potent D2 receptor antagonists, Parkinson's disease represents an absolute contraindication for this substance.

Dimenhydrinate

Dimenhydrinate is an antihistamine acting via the histamine-1 subtype. The recommended dosage is 1 mg/kg [33]. In clinical practice, typically the content of an ampoule (62 mg) is administered in adult patients. Dimenhydrinate regularly causes drowsiness and fatigue and should be used reluctantly in older patients due to the concomitant anticholinergic effects. In contrast, the substance in children (together with dexamethasone) is often the treatment of choice, not least because of the flexible application as juice, (sustained-release) tablet, or suppository.

Scopolamine

Scopolamine acts as an anticholinergic and is typically used as a transdermal therapeutic system in motion sickness ("scopolamine plaster") because of its very short plasma half-life, but can also be used for PONV prophylaxis [34, 35]. Due to the diffusion of the active substance through the skin, the scopolamine patch should be applied on the evening before the procedure or at least a few hours prior to anesthesia induction. Typical side effects are common and include dry mouth, dizziness, and fatigue in addition to blurred vision (especially when the patient displaces even small amounts of the drug into the eye), so patients with scopolamine patches are not fit to drive.

Indication for Antiemetic Prophylaxis

PONV impacts negatively the postoperative period—both in terms of subjective patient comfort and in terms of delays in postoperative convalescence. Increasingly, PONV is viewed as an avoidable side effect of surgery and anesthesia. Consequently, there is a trend toward routine, multimodal antiemetic prophylaxis. In view of the favorable side effect profile of the available antiemetic measures, a liberal prophylactic strategy can be justified (Fig. 21.4) [36]. Economic concerns have to be answered in such a way that there is probably no comparable intervention in modern medicine that can bring such a quality of life benefit to the patient with such low resource consumption. In addition, the processes in the postoperative period, both in the recovery room and especially on the peripheral care unit, are greatly simplified if PONV is avoided. In terms of a risk-to-benefit analysis, it has to be taken into account that an episode of nausea/vomiting leads to an average staff retention cost of about 18 € [37].

Accordingly, the importance of scoring systems in deciding whether prophylaxis should be carried out is increasingly taking a back seat in favor of liberal, general prophylaxis. Nevertheless, it is important to continue to make an individual assessment of the PONV risk in order to carry out extended therapy in high-risk patients, e.g., as add-on based on a general and routinely applied multimodal prophylaxis.

For clinical reasoning and for the sake of simplicity, it is reasonable to ascribe all presented antiemetic interventions a relative risk reduction of about 30%. With an increased risk of PONV in the presence of three risk factors (PONV risk ~60%), the administration of one single effective antiemetic will reduce the risk of PONV to 42% (60% − [0.3 ∗ 60%]). This simple calculation clearly highlights that any single prophylaxis is insufficient in high-risk patients. In a more detailed evaluation and taking into account the confidence of the evidence, differences between the substances and drug classes do exist, which may constitute the basis of a more tailored approach [38].

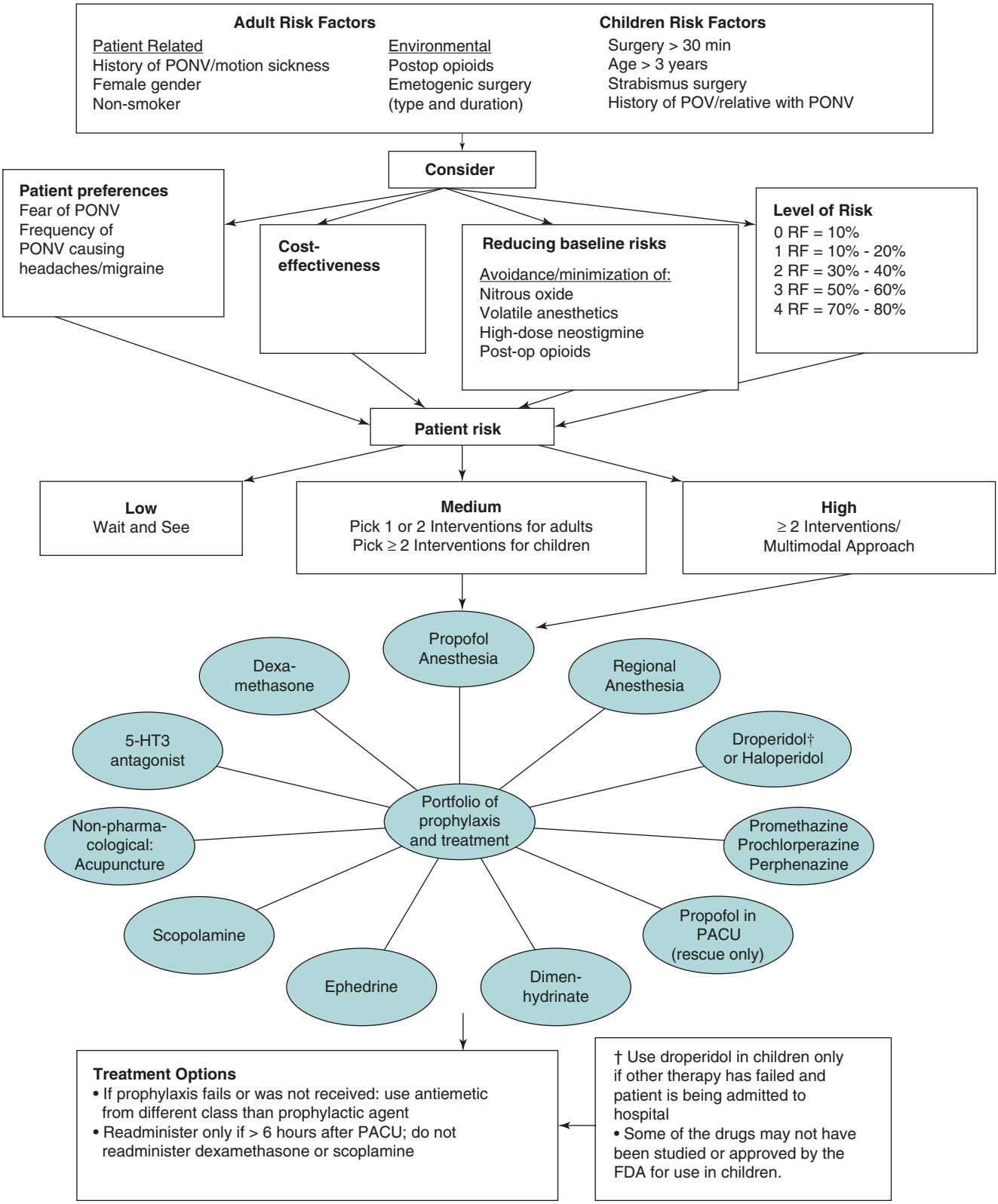

Fig. 21.4 Algorithm to address PONV, depending on the patient's individual risk and other factors. (Reprinted with permission from Gan et al. [36])

Our preferred option is to grant every patient a double antiemetic prevention—e.g., by administration of dexamethasone (4–8 mg) plus a "setron" (e.g., ondanseton 4–8 mg)—and then to adapt this general regimen in accordance to specific considerations, e.g., by adding a total intravenous anesthesia or additional pharmacological prophylaxis in case TIVA is not feasible.

Therapy of Nausea and Vomiting as well as Discomfort After Discharge

Depending on the vigor with which PONV is already treated prophylactically intraoperatively, the residual incidence of nausea and vomiting in the recovery room and after transfer of the patient to the peripheral wards will vary. Although there is an increasing assertion to perform a liberal prophylaxis, there will always be patients who still have PONV symptoms postoperatively. This may be due to a pharmacological prophylaxis that is too short-lived for the individual case, or simply due to a decrease in antiemetic protection in the later postoperative phase with concomitant trigger coming into play, e.g., opioids. The following principles apply to the treatment of these (residual) complaints:

- The therapy of PONV can be applied with the same drugs that are already discussed for prophylaxis.
- PONV therapy should be given as a combination therapy, i.e., at least as a two-drug combination from different pharmacological groups, if a subsequent PONV episode should be thoroughly avoided.
- PONV therapy should primarily be performed with drugs that have not been previously used for prevention in a single patient.
- Drugs from the drug group that have been previously administered should only be repeated if the time interval suggests a decrease in the initial effect.
- PONV therapy tends to require lower doses than those used for prophylaxis. However, practical considerations definitely support the use of "standard doses" for the prophylaxis and therapy of PONV.

Ultimately, the therapy of PONV is a secondary prophylaxis, because after an emetic event the probability of a recurrence is extremely high. There is only limited antiemetic therapy that can be administered to an ambulatory patient after discharge. Therefore, secondary prophylaxis must be particularly consistent and effective in these patients. Risk factors for a delayed occurrence of PONV are fairly similar to those of the predictive scores and include the following circumstances:

- Female gender
- PONV history
- Age <50 years
- Opioids used in the recovery room
- Occurrence of PONV in the recovery room

This score has been developed for outpatient procedures and helps in the decision for secondary prophylaxis or in the ambulatory setting to determine which drug, for example, an oral/sublingual antiemetic (e.g., ondansetron orodispersible tablet), should be prescribed. It further highlights the importance of effective therapy and secondary prevention if further treatment is impaired or limited, e.g., due to ambulation.

Conclusion

The choice of anesthetic technique and the pharmacological agents should be tailored to the needs of the patient as well as the type of procedure being performed as ERAS. The universally applicable goal for pharmacotherapy in enhanced recovery, which is valid for every class of intervention, is as follows: easy to use, associated with minimal side effects, maintaining homeostasis, allowing for a predictable onset and offset, and minimal impairment of recovery and function.

The pivotal role played by the anesthesiologist in facilitating the recovery process following surgical procedures has assumed increased importance in the concept of an enhanced recovery program. One of these important pillars that anesthesia could add to a working ERAS concept is a sufficient protection against the occurrence of PONV and a most efficient handling of PONV, if—despite prevention—it should occur in the postoperative period.

Since the antiemetic substances are without any doubt among the best-tested substances, it would be a missed chance if these agents are not being sufficiently used in order to improve a patient's wellbeing and speed up recovery.

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Early Oral Nutrition

22

Fabian Grass and Martin Hübner

Introduction

Three decades ago, postoperative starvation was common practice after most types of digestive surgical procedures. In particular, gastric decompression was performed until resolution of postoperative ileus [1]. This dogma was challenged with new evidence on the healing process of intestinal anastomoses, with increased collagen deposition and strength through early feeding [2, 3]. Further, a beneficial effect on wound healing was noticed [4]. A thorough first meta-analysis provided interesting new data suggesting a reduction in infectious complications, anastomotic leak rates, wound infection, and length of hospital stay, however, with an increased risk of vomiting among early fed patients [5]. Early enteral nutrition was part of the first published enhanced recovery series by Kehlet et al. of eight patients undergoing colonic resections [6]. Early feeding was combined with epidural analgesia, mobilization, and minimally invasive surgery to provide a "stress-free" surgical experience. Further studies confirmed these results, with early postoperative resumption of normal diet as an indispensable component of all early multimodal pathways [7–10].

The concept of early enteral resumption of nutrition has to be considered as part of a more global strategy, which aims to face increased metabolic demands and catabolism during surgery [11]. A comprehensive nutritional strategy needs to be launched preoperatively. Early screening for malnutrition and nutritional conditioning are mandatory (preoperative optimization). Omission of preoperative fasting—allowing a normal meal the evening before surgery and free liquids and carbohydrate loading until 2 hours prior to surgery—further contributes to decrease surgical stress. This approach allows keeping glucose levels stable by minimizing insulin resistance [12]. Early resumption of nutrition combined with stringent perioperative fluid management and early mobilization are thus a logical continuation of events. Noteworthy, several studies demonstrated a decline in postoperative nutritional status despite preoperative treatment in low- and high-risk patients, emphasizing the importance of early resumption of diet and timely launch of nutritional support if needed [13–15].

This chapter addresses the question why early enteral nutrition should be standard of care by reviewing available evidence according to type of surgery. Further, type of nutrition and criteria for nutritional supplementation in the postoperative period including enteral (tube feeding) and parenteral nutrition are reviewed.

Safety of Early Resumption of Diet

Oral nutrition including clear liquids can be initiated safely and immediately after surgery. This implies retrieval of nasogastric tubes by the end of the procedure, which has repeatedly been shown to be safe regardless of the type of surgery and even protective against pharyngeal and respiratory adverse events [16, 17]. A meta-analysis of randomized controlled trials of 2009 yielding 1173 patients did not find any drawback of early enteral nutrition [18]. Instead, a trend toward decreased postoperative medical and surgical complications and length of stay was observed. Even though the mechanism was not clear, early enteral nutrition within 24 hours was also associated with decreased mortality. The authors concluded that keeping patients "nil by mouth" is without any benefit and patients should be allowed to drink upon full recovery from anesthesia. Noteworthy, early postoperative feeding was also associated with increased vomiting [18]. A more recent randomized trial found a low residual

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diet to be more efficient compared to clear fluids in preventing nausea and promoting return of bowel function after colorectal surgery [19]. However, further ileus-preventing mechanisms within an enhanced recovery pathway helped to face these drawbacks of earlier experience [20].

Evidence in Surgical Subspecialties

Colorectal Surgery

The best evidence in favor of early resumption of enteral nutrition is available for patients undergoing colorectal surgery [21]. A systematic review of 14 randomized controlled trials described early enteral feeding after elective procedures, with 12 studies reporting almost exclusively or exclusively on patients undergoing lower gastrointestinal (GI) surgery. Seven studies reported adequately on the randomization process, whereas in the remaining studies the method of randomization was either unclear or not stated at all. Studies were heterogeneous regarding inclusion criteria, feeding policies, and reported outcomes. Most outcomes failed to reach statistical significance, but mortality and length of stay were decreased in the early feeding group. A further meta-analysis of 15 studies described a significant reduction of postoperative complications in the early feeding group, with no negative impact on anastomotic dehiscence or resumption of bowel function [22]. Individual randomized trials concluded that there was no reason to withhold early oral intake, since it was well tolerated without increasing rates of postoperative ileus, providing adequate ileus-preventing measures [23, 24]. The most recent meta-analysis providing data on 7 studies and 587 patients undergoing exclusively colorectal resections confirmed these results [25]. Hospital stay and total postoperative complications were decreased, while no significant impact on anastomotic dehiscence, pneumonia, or rate of nasogastric tube reinsertion was noticed.

Also less compelling than for colorectal surgery, the concept of early enteral nutrition embedded in an enhanced recovery pathway applies also for other types of surgery [26, 27].

Upper Gastrointestinal Surgery

A landmark randomized trial by Lassen et al. including 447 patients demonstrated feasibility of normal food at will after major upper GI surgery [26]. In particular, functional recovery, major complications, and length of stay were decreased in the group, which tolerated normal food at will from the first day after surgery, as compared to the "nil by mouth" and tube feeding groups. A recent meta-analysis showed further improved cellular immunity and decreased postoperative complications in gastric cancer patients undergoing major resections [28]. The meta-analysis of Willcutts et al. came to similar conclusions [29]: Early oral feeding was associated with shorter hospital stay, while no increase in relevant complications was observed. For esophageal cancer patients undergoing esophagectomy, improved nutritional parameters at the eighth day were observed in the early oral nutrition groups, and pulmonary complications and anastomotic leaks were decreased compared to patients receiving parenteral nutrition. Further studies on esophagectomy patients confirmed safety and feasibility of early enteral nutrition, by emphasizing in particular a restorative effect on intestinal barrier function postoperatively [30]. Early oral intake as part of standardized care pathways has also been recommended and endorsed by several societies after bariatric surgery [31–33]. As a common conclusion of most studies on upper GI surgery, early feeding is feasible and safe. However, more evidence particularly in the field of esophageal surgery is warranted.

Pancreatic Surgery

In particular after pancreaticoduodenectomy, the evidence is ambiguous. Malnutrition is preponderant among patients with pancreatic cancer, and morbidity rates of up to 40% after major pancreatic surgery, including specific complications such as delayed gastric emptying (DGE), request thorough identification and timely support of patients at nutritional risk [27, 34, 35]. Early normal diet according to tolerance is safe and feasible, according to several randomized trials and systematic reviews [26, 36–38], even in the presence of delayed gastric emptying or pancreatic fistulae [27, 39]. Hence, early normal diet at will and according to tolerance should be encouraged [40]. A combined approach of early enteral nutrition with parenteral nutrition might have to be considered in some patients unable to cover their needs by the enteral route alone [41]. In this latter study, patients with a combined nutritional strategy presented with lower infectious complications, reduced rate of gastric emptying, and improved liver function compared to the comparative group receiving solely parenteral nutrition. However, a recent randomized study showed an increased postoperative complication rate including pancreatic fistulae and discouraged early enteral nutrition through a nasojejunal tube. Hence, an individual approach based on patients' nutritional status, disease presentation, and expected postoperative course should guide postoperative support strategies when normal diet at will is not sufficient.

Hepatic Surgery

In the multicenter trial of Lassen et al., 66 patients underwent liver surgery, with the aforementioned beneficial outcomes in the early nutrition group confirming its safety after major hepatic resections [26]. A randomized controlled trial by Hendry et al., combining early oral administration of nutritional supplements with administration of laxatives, accelerated bowel recovery, however, without shortening hospital stay [42]. These results of accelerated functional recovery in early fed patients were confirmed by a meta-analysis, which further demonstrated decreased infection rates and improved immune competence and concluded early enteral nutrition to be safe after liver resection [43].

Nutritional Supplementation Strategies

As discussed above, free diet should be aimed for starting from the first postoperative day. The amount of oral initial intake should be tailored to individual tolerance, since resumption of a normal everyday diet by the second postoperative day may not be an achievable goal for every patient [22, 44, 45]. Hence, energy needs might not be covered by free diet alone, since oral intake was shown to rarely exceed 1200–1500 kcal per day [46]. Oral nutritional supplements (ONS), in particular immunonutrition, may thus need to be considered to cover additional metabolic needs. According to recent European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines [47], perioperative nutritional supplementation should be initiated if it is anticipated that patients are:

- Unable to eat for more than 5 days after surgery
- Unable to maintain above 50% of recommended intake for more than 7 days

Enteral nutritional support needs further strong consideration in patients at severe nutritional risk, which has been defined as follows by the ESPEN working group (2006):

- Weight loss >10–15% within 6 months
- Body mass index <18.5 kg/m^2
- Nutritional Risk Score (NRS 2002) >5
- Hypoalbuminemia (<30 g/L) with no evidence of hepatic or renal dysfunction

All parameters reflect undernutrition and disease-associated catabolism [48–50].

In all patients fulfilling the aforementioned criteria, nutritional therapy should be started independently of the type of surgery, and the enteral route should always be preferred (Fig. 22.1) [47]. Early tube feeding with standard whole protein formulas, either through a nasojejunal tube or a catheter jejunostomy for long duration, has to be considered within 24 hours of surgery in patients undergoing head and neck surgery or severely traumatized or brain injured patients [51, 52]. Several historical and more recent large-scale randomized controlled studies confirmed the superiority of the enteral route in preventing infectious complications, length of stay, and costs across all types of surgery [13, 48, 53–55]. Regarding the postoperative situation, the European and American guidelines [47, 56] recommend initiating postoperative nutritional supplementation within 24 hours. This is even more important considering that postoperative nutritional status deteriorates *despite* nutritional supplementation [15].

Postoperative Immunonutrition

The evidence regarding immune-enhanced nutrition (arginine, glutamine, omega-3 fatty acids, and nucleotides) is somewhat ambiguous [47, 57]. While a beneficial effect on postoperative outcome was repeatedly shown in patients undergoing major cancer surgery, studies differed considerably regarding regimens, control groups, and outcomes, and a recent study revealed potential industry bias [58]. Further, the optimal timing could not be defined beyond doubt [59]. As a general rule, preoperative supplementation for 5–7 days should be considered in patients at nutritional risk according to standard definitions or screening tools, i.e., Nutritional Risk Score (NRS) or Malnutrition Universal Screening Tool (MUST) [50, 60]. However, more recent evidence also supports the administration of postoperative immunonutrition [46, 59, 61, 62]. While a randomized controlled trial of Klek et al. failed to demonstrate any clear advantage of routine postoperative immunonutrition [63], two recent studies by Moya et al. showed a significant decrease of medical and surgical infectious complications [64, 65]. Because of its cost-efficiency compared to parenteral administration, enteral immunonutrition was endorsed by recent ESPEN recommendations based on the principle of no harm [47] and has to be strongly considered in malnourished patients undergoing cancer surgery [66].

Parenteral Nutritional Supplementation

The following contraindications to enteral nutritional support may warrant the use of parenteral support strategies [47]:

- Ileus
- Severe shock
- Intestinal ischemia
- High-output fistula
- Severe intestinal hemorrhage

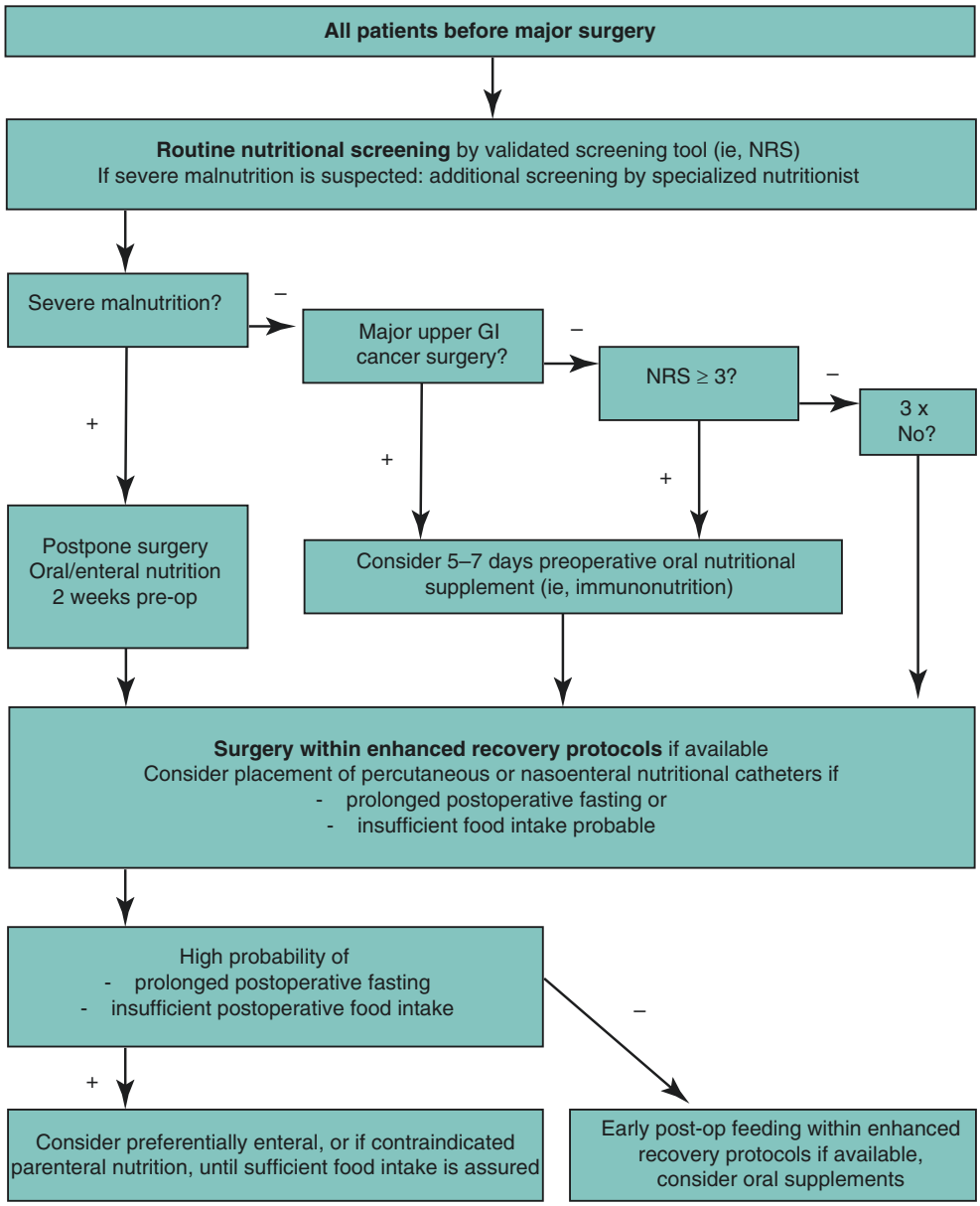

Fig. 22.1 Suggested treatment algorithm for nutritional support of surgical patients. NRS Nutritional Risk Score, GI gastrointestinal

Chen et al. presented a meta-analysis of randomized controlled trials to confirm safety and efficacy of parenteral nutrition [67]. Interestingly, an effect on leukotriene synthesis in patients with fish-oil-supplemented parenteral nutrition was observed. These findings were confirmed more recently in severely ill intensive care unit patients, especially regarding a modulated postoperative immune response [68–70].

As a common conclusion, postoperative parenteral nutrition should only be considered in patients who cannot be adequately fed enterally or who present the aforementioned contraindications [47].

Conclusion

There is overwhelming evidence to support early resumption of a normal enteral diet, which should be the standard of care after most types of surgery. Specific criteria upon nutritional screening should guide clinicians in deciding whether nutritional support is warranted, especially in malnourished and cancer patients. The enteral route should always be the first choice; however, parenteral nutrition might be indicated in some circumstances when enteral supplementation is not feasible or sufficient.

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Early Ambulation and Physiotherapy After Surgery

23

Thomas W. Wainwright and Louise Burgess

Introduction

Physiotherapists play an important role within the surgical multidisciplinary team by encouraging early ambulation and promoting a return to function for patients. Early ambulation is an important contributor to the prevention of early postoperative complications such as respiratory infections [1] and venous thromboembolism [2] within ERAS pathways. Following surgery, patients often have impaired muscle function, either due to inhibition as a result of pain and swelling or atrophy due to immobility and bed rest. Unimpaired muscle function is essential to enable a patient to complete activities such as walking, rising from a chair, or climbing stairs. These activities are important functional tasks that allow for physical independence and are often essential in fulfilling discharge criteria from hospital. Therefore, the inability to complete activities of daily living postoperatively can delay early postoperative recovery and the achievement of discharge criteria, as well as impacting on return to function following discharge. Thus physiotherapists play an essential role in an ERAS surgical pathway. This chapter will discuss the role of early ambulation and postoperative physiotherapy within Enhanced Recovery After Surgery (ERAS) pathways across the surgical specialties.

Early Ambulation

Early postoperative ambulation is a fundamental principle of good physiotherapy practice and is important physiologically, to prevent pulmonary and hemodynamic complications postsurgery and to accelerate the achievement of discharge criteria. Prolonged bed rest after surgery is believed to be an important risk factor of postoperative complications and morbidity; therefore, enforced early ambulation is strongly recommended by the ERAS Society, across a number of surgical subspecialties [3–13]. Definitions of early ambulation can vary between healthcare providers. However, generally, mobilizing a patient involves activities such as sitting, standing, walking, or passive exercises performed by a physiotherapist, initiated on the day of surgery, with the aim of preventing muscular and cardiovascular deconditioning and complications attributed to immobility [14]. Early ambulation has been shown to reduce the length of stay following major surgery and to decrease the rate of postoperative pulmonary complications, venous thromboembolism, and infection [15]. Extended or incomplete postoperative recovery often increases medical costs and can be associated with a sustainable indirect burden to patients [14], creating a strong case for implementing early mobilization as part of postoperative care.

However, the research evidence to support the implementation of early ambulation among the majority of ERAS guidelines is reported as low by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria, due to the use of extrapolated data from other surgical procedures, the weak directly proven causal effect, or there being limited or poor methodological supporting studies [3–13]. Poor compliance to ERAS protocols is mostly observed in the postoperative period [16], and despite the widely recognized importance of early ambulation as part of ERAS programs, it is also often found that adherence to early ambulation remains low [14]. The reported barriers to early ambulation are wide ranging and may include patient, structural, and cultural factors. However, such barriers may also have potential solutions that could be implemented to increase compliance (Fig. 23.1). While some deviations from the standardized pathway may occur due to medical necessity, it should be recognized that a quarter of noncompliance cases are reported to be amendable [16]. It has been reported that the achievement of early ambulation requires substantial time for hospital staff, and therefore the

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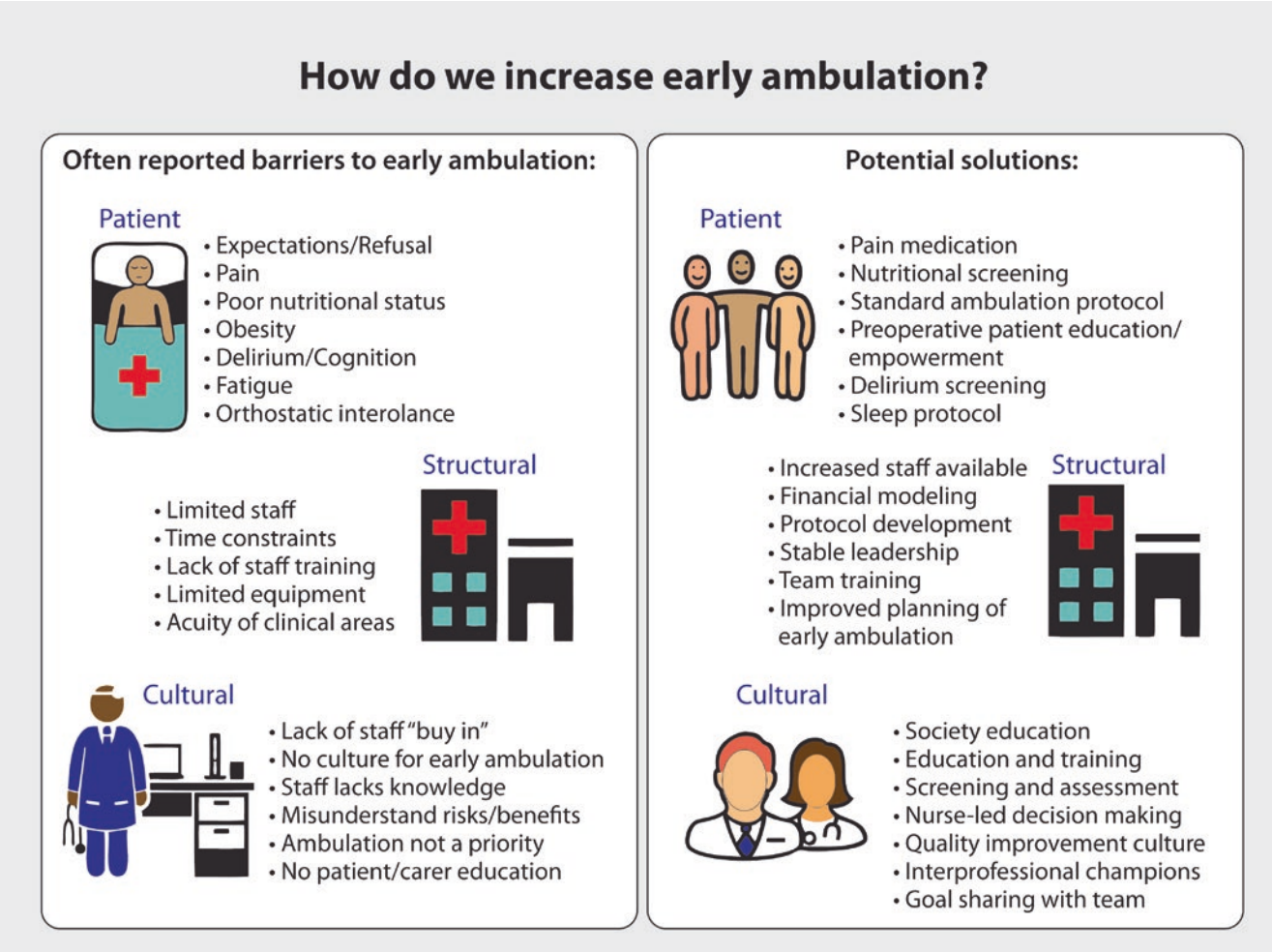

Fig. 23.1 Early mobilization infographic

lack of available manpower and the requirement of patient and family involvement are reported to be barriers to compliance [17].

Early Ambulation in Surgical (Nonorthopedic) Pathways

There is emerging but limited evidence for early ambulation in surgical pathways. Regardless of the techniques used to facilitate ambulation, avoiding bed rest is reported to be an essential factor in preventing postoperative complications, improving functional capacity, and reducing length of hospital stay in patients after cardiac surgery [18]. Early ambulation programs based on supervised exercises are feasible for patients undergoing major elective abdominal oncology surgery and are also reported to improve functional capacity [19]. The beneficial effects of early postoperative ambulation are well established in colorectal pathways, with improved adherence to a standardized ERAS protocol, including early mobilization (patients to be out of bed for 2 hours on the day of surgery and for 6 hours per day until discharge [20]) associated with improved clinical outcomes, indicating a dose-response relationship [21]. Early ambulation is feasible in patients following gastrointestinal surgery and is encouraged for reducing postoperative pulmonary complications [22]. Torres Lacomba et al. [23] report the effectiveness of an early physiotherapy intervention for women who had breast cancer surgery for preventing secondary lymphedema for at least 1 year after surgery. The patients received manual lymph drainage, massage of scar tissue, and progressive active- and action-assisted shoulder exercises and were compared to those receiving educational strategy only. Early ambulation is also recommended in ERAS Society guidelines for rectal/pelvic [11], pancreatic [6], liver [13], and head and neck surgeries [8]; however, there is a need for prospective studies to establish the "dose" of mobilization.

An ERAS pathway for patients undergoing pancreaticoduodenectomy [24] reports those receiving ERAS care to have an earlier recovery of mobilization, oral feeding, gut

mobility, and an earlier suspension of intravenous fluids. However, adherence to postoperative early ambulation targets was reported to be just 47%. A subgroup analysis highlighted that 71% of those with early postoperative low compliance with ERAS pathways had complications, emphasizing the need for adherence to programs.

Interestingly, an investigation into the reasons for noncompliance to ERAS protocols in colorectal surgery reports compliance to mobilization on the day of surgery to be around 40%, although approximately 93% of the cases of noncompliance were justified due to medical necessity [16]. Similar values are reported by Gustafsson et al. [21], whereby only 48.4% of all colorectal patients included within their study were out of bed for 2 hours on the day of surgery and 27.5% were out of bed for 6 hours after postoperative day 1. Early ambulation compliance has been compared between colorectal patients receiving standard ERAS care and those on a facilitated mobilization ERAS pathway [14]. A healthcare professional visited the patient on the day of surgery to reinforce their mobilization goals and to assist with the transfer to a chair, and then three times per day from postoperative day 1 to 3 (or discharge) to reinforce mobilization goals, assist with transfer, and walk with the patient. Self-reported day of surgery mobilization was recorded as 36% for patients receiving usual ERAS care and 72% for patients on a facilitated mobilization program; however, in this study, adherence to mobilization did not improve patient outcomes.

Slightly better compliance is reported within a 6-year thoracic ERAS program, with 61.5% of patients achieving their target goal of a 250-foot assisted ambulation within 1 hour of extubation [25]. The target goal was achieved at a greater rate in the late patient group (72%) compared to the patients within the first 2 years of the program (37%), which the researchers attribute to the impact of the learning curve and protocol adoption over time. Family engagements, setting rigorous expectations and collaboration from nursing, anesthesia, and administration staff were reported to be important factors to successful compliance [25]. Better compliance to early ambulation is also reported within an enhanced recovery after liver resection program [26], whereby 77.6% patients managed to sit out of bed on postoperative day 1 and 79.3% started walking with the assistance of a physiotherapist by day 2. Achieving early ambulation and early removal of urinary catheters were important factors in achieving a successful ERAS pathway and early discharge following liver surgery; however that success required the avoidance of postoperative complications [26].

Although actual compliance rates are not reported, early ambulation and preoperative carbohydrate drinks were the only individual elements of an ERAS protocol for resection for primary lung cancer that were predictive of reduced morbidity or length of stay [27]. Elements of the ERAS pathway that positively influenced early ambulation were reported to be postoperative nausea and vomiting control, avoidance of epidural analgesia, a standardized analgesia regime with avoidance of opiates where possible, and avoidance of fluid overload [27].

There is a strong, theoretical case for implementing early ambulation following major surgery, and regardless of the techniques used as mobilization (i.e., moving from a supine position to upright sitting, standing, and walking postures), avoiding bed rest is reported to be an essential factor in preventing postoperative complications, improving functional capacity, and reducing length of stay in hospital. Despite this, actual reported compliance to ambulation protocols is low, and a greater adherence to programs may demonstrate additional benefits for patients and healthcare providers. Further future research to elucidate the physiological benefits of early ambulation and its effect on reducing morbidity postoperatively may help to increase compliance to early mobilization protocols.

Avoidable Common Barriers to Early Mobilization

In order to achieve early, postoperative ambulation, it is first important to identify the reasons why it is not currently occurring, and the barriers within the given context. Ensuring that patients ambulate following surgery requires multidisciplinary support and interdisciplinary collaboration in order to address one or a combination of patient, structural, or cultural barriers to early ambulation. While some patients are unable to mobilize early, due to a justifiable medical reason, many potential barriers to early mobility protocols can be controlled. For example, in a context where patients refuse to mobilize due to a lack of confidence or due to anxiety, a comprehensive preoperative education or empowerment session could be delivered to set ambulation expectations and individual goals. Similarly, preoperative screening for frailty, delirium, anemia, and poor nutritional status can help to identify patients with a known higher risk of delayed ambulation.

Postoperatively, acute pain is one of the major causes that affects recovery after surgery, and therefore choosing a multimodal, opioid-sparing analgesic regime in combination with regional nerve blocks or wound infiltration may provide a faster recovery and enable early ambulation [28]. In addition, the early removal of drains and catheters is also a supporting element of ERAS pathways that can facilitate early ambulation. Implementing small organizational changes, such as providing patients with comfortable chairs, walking frames, and ambulation diaries, can also increase motivation to mobilize.

Early Ambulation in Orthopedic (Hip and Knee Replacement) Surgery

The benefits of early postoperative ambulation are better established for orthopedic patients. There is evidence that ambulation on the day of surgery as part of an ERAS pathway reduces length of stay [29, 30], along with the incidence of thromboembolic complications [31] and need for blood transfusion [32], and does not increase the risk of postoperative complication or adverse events [33]. For example, a prospective cohort study (n = 136) [34] investigating the effect of physiotherapy on length of stay for hip and knee replacement patients found that patients who received physiotherapy on the day of surgery had a shorter hospital stay than those having physiotherapy the following day (2.8 days ± 0.8 days vs 3.8 days ± 1.7 days).

Since early ambulation is essential, factors that prevent its occurrence—such as pain and the problem of early postoperative orthostatic intolerance—are important. Optimal pain management is a prerequisite for early ambulation. While the often-favored nerve-blocking techniques may provide pain relief, more simple systemic techniques such as the combination of a Cox-2 inhibitor, with paracetamol, and high-dose preoperative glucocorticoid administration can provide analgesia, a reduction in fatigue, and no motor block, thereby improving the early recovery profile of the patient and enabling an optimal start for the functional recovery [35].

While pain may be managed effectively in most patients (except for certain high-pain responders: pain catastrophizers, preoperative opioid users, sensitized patients), the problem of orthostatic intolerance is yet to be solved. Data show that an undesirable shift in autonomic nervous system function toward increased parasympathetic function and loss of sympathetic stimulation especially to the lower legs occurs [36], and techniques to mitigate the problem, such as optimized fluid management, have not worked. The use of drugs such as midodrine needs further study [36].

Early Ambulation and Physiotherapy for ERAS Patients Within the Intensive Care Unit

A patient may be admitted to an intensive care unit (ICU) after elective major surgery if they require postoperative support either due the complexity of surgery or because of coexisting medical conditions. ICU admission is not always required among all major surgeries that adopt ERAS principles, with orthopedic procedures generally being the most well tolerated by patients and consequently rarely requiring ICU admission [37]. ERAS guidelines highlight that gynecologic, cardiac, pancreaticoduodenectomy, colorectal, hepatic, and head and neck cancer patients may require a transfer to an ICU, depending upon their condition following surgery.

The role of physiotherapy within ERAS and rehabilitation following intensive care is important. There is limited research available that focuses on the effect of an ERAS program on outcomes for patients discharged from an ICU following elective major surgery; however, this cohort may have the most to gain from a multimodal approach that integrates evidence-based interventions. Critical care physiotherapists adopt roles that assimilate strongly with key ERAS principles, and they can play a vital role in ensuring patients remain on track with their ERAS pathway while in an ICU. The aim of physiotherapy treatment provided within ICU can be broadly separated into two: interventions to improve respiratory function and early initiation of the rehabilitation process.

Patients in an ICU may require mechanical ventilation to help their breathing; however, this can lead to pulmonary complications. Respiratory physiotherapy involves early ambulation or mobilization where possible, the repositioning of patients within bed to optimize respiratory function, and the utilization of manual techniques or the manipulation of ventilator settings to clear lung secretions that build up within the lungs, when mobility and consequently deep breathing are limited. This helps to reduce the risk of pulmonary issues. The early initiation of the rehabilitation process may focus on maintaining range of joint motion to prevent contractures, depending on the length of ICU stay, and exercises to reduce muscle atrophy due to immobility. As soon as the patient is able, the physiotherapist will progress mobilization activities to sitting, standing, and then walking, in order to facilitate their transfer out of ICU and their first steps to regaining full physical function. Patients can become weak quickly, and the use of exercises, electrical stimulation, and ambulation practice can reduce muscle atrophy and joint stiffness that may occur.

Despite the publication of safety recommendations and clinical practice guidelines, the implementation of early mobilization remains a challenge for patients admitted to ICU following surgery [38]. As with early ambulation in the general ward, barriers are reported to be related to unit culture, a lack of resources, prioritization, and leadership [39]. Better adherence to sedation and mobilization protocols, clinical leadership, and increased staff resources and training can help to address both clinical and logistical factors that preclude early ambulation in a high-dependency setting [38]. In addition, reorganizing management practices and developing strategies to encourage interdisciplinary collaboration will likely facilitate compliance to mobility protocols in this context.

Once patients are transferred from the ICU, providing a more intense, coordinated rehabilitation program for patients, delivered by a specialized physiotherapist and supported by a multidisciplinary team, is hypothesized to improve recovery [40]. Logistical factors must also be considered, so that

there are an adequate number of well-informed physiotherapists who are able to utilize a standardized rehabilitation program and ERAS pathway documentation [41].

Postoperative Physiotherapy

The future focus of ERAS pathways is not only to accelerate the achievement of discharge criteria but also to consider how a patient can return to normal function and physical activity quicker following surgery. Therefore, it is important to consider which modalities of physiotherapy and rehabilitation can be effective within the postoperative stage (during hospital admission and after discharge) of ERAS pathways. The role of prehabilitation is examined in Chap. 10 within this textbook. Although early ambulation is well established in ERAS pathways, debate remains regarding what is the optimal postoperative physiotherapy regime for accelerating achievement of discharge criteria and return to function following surgical procedures. There is currently no firm evidence base for a single type of exercise-based physical rehabilitation to enhance postoperative recovery in the "average" patient, and evidence is limited across all specialties.

Postoperative Physiotherapy in General Surgery

ERAS is well established in improving patient outcomes and reducing hospital costs following general surgical procedures; however, the current evidence for postoperative physiotherapy interventions tested within ERAS cohorts is poor, and there is a pressing need to highlight and expose this [42]. There is evidence that the implementation of individualized perioperative training is tolerable and worthwhile [43]; however, the effectiveness of postoperative physiotherapy is still under debate. In fact, the current evidence base for postoperative physiotherapy within general ERAS pathways is limited to just one high-quality randomized controlled trial (RCT) specific to cystectomy [44].

The study compared standard fast-track surgery ($n = 57$) to fast-track surgery with the addition of an exercise-based intervention ($n = 50$), following radical cystectomy [44]. The postoperative intervention included early ambulation, set goals for mobilization and walking, an exercise-based intervention, and a physical therapy twice a day for the first 7 postoperative days, followed by a standardized supervised progressive muscle strength and endurance training program. The progressive exercise program was performed for two 30-minute sessions a day, supervised by a specialist physiotherapist, and was documented by patients in diaries. The authors found that postoperative mobilization was significantly improved by walking distance ($P \leq 0.001$), and the ability to perform functional activities was improved by 1 day ($P \leq 0.05$). The median length of stay was 8 days in both groups ($P = 0.68$), and there were no significant differences between treatment groups in severity of complications.

A secondary analysis by the same authors on their previously completed RCT found no overall impact on global health-related quality of life (HRQoL) following the intervention but significant and positive impacts of HRQoL aspects related to bowel management and respiratory function (improvement to dyspnea [$P < 0.05$], constipation [$P < 0.02$], and abdominal flatulence [$P \leq 0.05$] scores), highlighting the benefits of multimodal rehabilitation, including physical exercises in fast-track radical cystectomy. In contrast, the standard care group reported reduced symptoms in sleeping patterns ($P \leq 0.04$) and clinically relevant differences in fatigue, body function, and role function [45].

It is not surprising that historical evidence for postoperative physiotherapy from across surgical specialties in non-ERAS cohorts is better established. While this evidence is valid, patients are now recovering much quicker postsurgery with ERAS, and as such the ability to mobilize patients early is markedly different than historical care and in non-ERAS cohorts. Therefore, we cannot be sure that the same physiotherapy interventions will be effective or required for both cohorts, as there will be physical and logistical differences between patients. An aim of ERAS is to reduce the surgical stress response for the patient, and most studies do not consider the multimodal approach (including regional anesthesia, minimally invasive surgical techniques, early feeding, and multimodal opioid-sparing analgesia) that may impact postoperative outcomes.

Related research has proposed the use of supervised physiotherapy to accelerate recovery from surgery, including complex rehabilitation programs [46], aerobic training [47, 48], weight loss and diet interventions [49], stretching [50–52], and lymphatic drainage techniques [53]. Such ingredients of a multifactorial physiotherapy program should be trialed within suitable cohorts of ERAS patients so that intraoperative procedures and the individual pathophysiology of the procedure in which it is being tested can be considered.

Postoperative Physiotherapy in Orthopedic (Hip and Knee Replacement) Surgery

Evidence-based interventions applied before and after total hip and knee replacement (THR/TKR) have been previously investigated, and although evidence suggests high-volume, preoperative exercise may enhance postoperative recovery, it has been difficult to demonstrate superiority of one type of exercise over another [54].

Following THR and TKR, increased early loss of lower leg muscle function (30–80% after THR and TKR, respectively) can lead to delayed post-discharge recovery. Progressive strength [55] and higher intensity rehabilitation training programs [56] can help to ameliorate postoperative deficits in muscle strength. However, the underlying mechanisms for this reduced muscle function are still to be understood, and further research is required to instruct the choice of effective rehabilitation techniques [54]. Despite significant efforts to improve rehabilitation, the use of preoperative exercise, traditional physiotherapy regimes, and earlier initiated and more intense postoperative strengthening regimes have all been found to have a limited effect in the "average" patient [57, 58]. Home-based exercise or community-based intervention classes—supported by new technologies, such as wearable activity trackers—to support exercise compliance and improve the cost-effectiveness of postoperative rehabilitation may have a greater benefit to patients [54].

Future work should therefore consider which therapeutic interventions are effective, and for which groups of patients. Preoperative characterization of patients at risk of a delayed recovery due to their pain status, frailty, psychological status, socioeconomic status, and unrealistic expectations of recovery should be pursued. In this context, functional outcome measures should be used—given the discrepancies seen when patient-reported outcome measures (PROMs) are compared to objective measures of functional performance and physical activity—in the early recovery phase [59] and in the longer term [60].

Conclusion

Recovery of a patient's physical fitness within the postoperative period is important to reduce the likelihood of poor functional outcomes and postoperative complications and should be a focus of future service development and research within ERAS. All patients could benefit from personalized, physiotherapy care plans in the days and weeks following surgery; however, this may not be economically feasible. Therefore, it is not only important to ensure that the physiotherapy that is delivered postoperatively contains the optimal ingredients for recovery but also to analyze economic and clinical outcomes, so that those patients who need rehabilitation are targeted. As such, there is a need to identify high-risk adults or those with a need to regain a required level of function (those returning to work or sport), so that individualized, high-intensity rehabilitation programs can be created.

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Postoperative Multimodal Pain Management

24

Hans D. de Boer

Introduction

In the past 40 years, the knowledge and management of acute postoperative pain have been improved significantly. Many strategies have been developed and employed that led to the development of national and international clinical practice guidelines for management of acute postoperative pain [1]. Despite these efforts, the prevalence of postoperative pain remains high, as at least half of the patients report moderate-to-severe pain at the time of discharge [1].

Knowledge of the neurobiology of nociception is essential in order to understand the pathophysiological changes induced by surgery. Nociception induced by surgery is a complex and multifactorial process, as surgery results in tissue injury with consequent release of histamine and inflammatory mediators such as peptides (e.g., bradykinin), lipids (e.g., prostaglandins), neurotransmitters (e.g., serotonin), and neurotrophins (e.g., nerve growth factor). These mediators activate peripheral nociceptors, which initiate transduction and transmission of nociceptive information to the central nervous system (CNS) [1, 2]. A more detailed overview on pain physiology and pain pathways is provided in Chap. 15.

In ERAS pathways adequate postoperative pain relief is, together with all other ERAS elements, important in order to improve the quality of perioperative care and reduce postoperative length of hospital stay [3, 4]. Adequate management of postoperative pain leads to attenuating surgical stress and maintaining postoperative physiological functions. In fact, antinociceptive strategies should ideally be initiated in the intraoperative period already and be a continuum postoperatively in order to have adequate postoperative pain relief and improved outcome [3, 5]. Furthermore, opioid-sparing analgesic strategies—including regional analgesia techniques as part of multimodal, evidence-based, and procedure-specific multimodal pain management—should be implemented as a standard of care [3, 5, 6].

Acute and Chronic Effects of Postoperative Pain

Postoperative pain may lead to a delay in postoperative recovery. Moreover, when postoperative pain is not treated adequately, it results in undesired acute and chronic effects. Reduction of nociceptive input to the central nervous system by adequate perioperative analgesia results in improved recovery and reduction of complications and length of hospital stay [1, 3–6].

Acute Effects of Pain

Local tissue injury as a result of the surgical incision results in activation of different cascades leading to the release of neurotransmitters, stress hormones, catecholamines, and inflammation products and many other pain-induced related products [1, 2]. This leads to a disbalance in sympathetic and parasympathetic outflow, neuroinflammation, and a situation of whole body end-organ dysfunction [5, 6]. Sympathetic activation increases the oxygen consumption and may decrease the myocardial oxygen supply through coronary vasoconstriction, which increases the risk of the development of myocardial ischemia and infarction [1, 2, 5, 6]. Furthermore, the sympathetic activation delays the return of gastrointestinal motility, which may result in postoperative ileus [5]. As understood from the nociceptive pathways described in Chap. 15, multiple target areas can be identified on which antinociception can be applied in order to block or mitigate nociceptive signaling processing and transmission [2, 7]. The scientific rationale for a multimodal or more precise multitarget analgesia approach is based on the multifactorial nature and complexity of the nociceptive pathways that

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are activated by surgery [2, 7]. The large variety of pathophysiologic responses initiated and maintained by nociceptive input are among others responsible for acute postoperative pain [2, 7]. Uncontrolled postoperative pain is detrimental, which contributes to increased complications and even morbidity and mortality [1]. Besides the neuroendocrine stress response, which affects the central nervous system, other areas of the body are affected as well. The metabolic response may lead to hypercoagulability, which consists of enhanced coagulation, inhibition of fibrinolysis, increased platelet activity, and plasma viscosity [2, 3, 5]. This state of hypercoagulability increases the risk of myocardial ischemia and infarction, vascular graft failure, and deep venous thrombosis. Furthermore, hyperglycemia as a result from the surgical stress response leads to impaired wound healing, catabolic state, and depression of the immune function [2, 5]. Another important negative effect of the stress response to postoperative pain is an impaired respiratory function [1, 5, 6]. Especially in upper abdominal and thoracic surgery, spinal reflexes are inhibited leading to a decrease in phrenic nerve activity [1, 5]. Furthermore, when patients suffer from pain postoperatively, insufficient respiration and inadequate cough function increase the risk for postoperative pulmonary complications [1, 5]. Therefore, attenuation of postoperative pain is essential in order to facilitate enhanced recovery after surgery (ERAS) and to reduce perioperative complications and morbidity and mortality.

Chronic Effects of Pain

Acute and uncontrolled postoperative pain may lead to chronic postoperative pain. Chronic postoperative pain is not very well recognized as the incidence of chronic postoperative pain resulting from surgery is high, 10–65%. Of these patients, 2–10% experience severe chronic postoperative pain [1]. Therefore, poorly treated postoperative pain is a predictive factor in the development of chronic postoperative pain.

Although we know that the transition from acute to chronic postoperative pain occurs very fast, the mechanism of action is poorly understood [1, 5]. The severity of acute postoperative pain is an important predictor of chronic postoperative pain, but other factors—such as type of surgery, areas of postoperative hyperalgesia, and ongoing nociceptive stimuli, which can begin perioperatively and continue long into the postoperative recovery period—are important to recognize as risk factors for development of chronic postoperative pain. Therefore, adequate control of acute postoperative pain by applying postoperative multimodal analgesia is important to prevent chronic postoperative pain [1, 2, 7–9]. Furthermore, adequate pain control is essential in enhanced recovery pathways in order to reduce complications and morbidity and mortality and maybe even to improve the long-term outcome [1, 9] (Fig. 24.1).

Preventive Analgesia

Preventive analgesia, previously called preemptive analgesia is a antinociceptive treatment or intervention that precedes a surgical intervention leading to surgical stress (incisional and inflammatory injury) and that attenuates pain from high-intensity nociceptive stimuli before, during, and after induction of the surgical stress [1, 9]. In fact, the goal of preventive analgesia is to attenuate afferent input produced by the peripheral nervous system that can alter peripheral and central sensory processing. This surgical stress due to tissue injury induces changes in the peripheral afferent neuron and spinal cord, which results in an extended period of excitability [1, 5, 7, 8]. This hypersensitive state, which can exist from days to months, will lead to acute postoperative pain and eventually, when not treated adequately, chronic pain after surgery. Therefore, central sensitization and excitability can develop after surgery in patients without a history of preoperative pain [2, 7, 8]. However, when a patient may already have acute or chronic pain developed, central sensitization is already existing before surgery. These particular patients with preexisting pain may have even more intense pain in the postoperative period and are prone to develop chronic postoperative pain [1, 2, 8]. There are two phases in which the noxious stimuli are responsible for the hypersensitive state: the primary phase in which the noxious stimuli are related to the surgical injury, e.g., tissue injury, and the secondary phase in which the ongoing noxious stimuli are produced by the release of various different chemical mediators, including stress mediators and inflammatory mediators, from damaged tissue. The secondary phase can begin during surgery but can extend long into the postoperative period and lead to postoperative pain. The duration of the postoperative recovery period depends upon various factors, such as type and length of surgery, comorbidities, immunological status, nutritional status, and psychological profile [3, 5, 6]. Therefore, it is important to treat the two phases to prevent unrestricted afferent input that causes central sensitization and concomitant postoperative acute and chronic pain after surgery. Although several experimental studies support the concept of preventive analgesia, the results of human studies are inconsistent. Further dedicated studies are needed to investigate blockage of all the noxious stimuli within multimodal analgesia strategies.

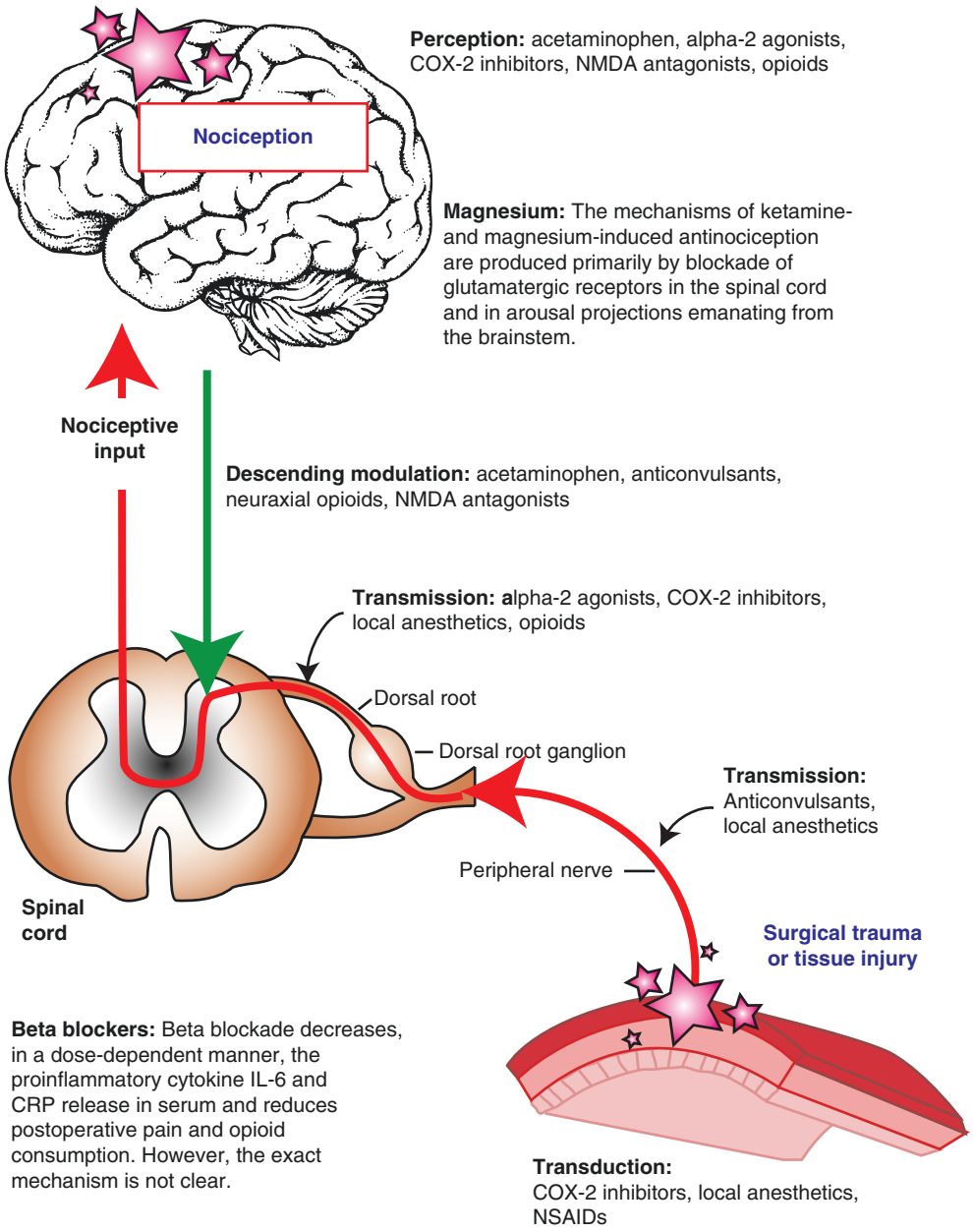

Fig. 24.1 Multimodal analgesia mode of action

Multimodal Pain Management Strategies

The scientific rationale for a multimodal or more precise multitarget analgesia approach is based on the multifactorial nature and complexity of the nociceptive pathways that are activated by surgery [5–10]. Multimodal or multitarget analgesia to control nociception with different classes of drugs, each acting on one or more targets (see Fig. 24.1), will be the future in anesthesia and ERAS pathways in order to prevent nociceptive stimuli affecting the central nervous system, reduce surgical stress, and prevent postoperative pain developing [2, 7–10]. In this manner the antinociceptive benefits of controlling acute postoperative pain can be optimized. Moreover, adequate treatment of acute postoperative pain allows for better control of the postoperative pathophysiology and facilitates enhanced recovery, early mobilization, early nutrition, and reduction of length of stay (LOS) [2–9]. Widespread implementation of multimodal pain management requires a multidisciplinary approach and a change in traditional care [3–7]. However, the combination of these pain management strategies, together with the other enhanced after surgery elements, has the potential to reduce complications, improve outcomes, and reduce morbidity and mortality [3–6]. In the next sections, a more detailed overview is given on different drugs that can be used in postoperative multimodal pain management.

Opioid Analgesia

Opioids remain an important cornerstone for the treatment of postoperative pain and are the most frequently prescribed class of drugs globally [1, 9]. However, it is also recognized that opioids are related to undesirable side effects and drug abuse problems. Opioids produce a reliable pain relief in surgical and nonsurgical patients. Furthermore, opioids are an integral part of a multidisciplinary approach to management of acute and chronic postoperative pain [1, 2, 7, 9]. However, opioid-sparing or even opioid-free techniques are important in enhanced recovery pathways to allow patients to recover early and to reduce complications related to opioid use [2, 3, 7, 10, 11].

Opioids generally exert their analgesic effects mainly through μ(mu)-receptors in the CNS, although opioids may also act at peripheral opioid receptors [1, 9, 12–14]. Moreover, it was shown [9–14] that opioids target multiple classes of opioid receptors in the periaqueductal gray, spinal cord, amygdala, rostral ventral medulla, and cortex [9, 12–14]. Binding to these receptors prevents or disrupts information transmission in the nociceptive systems by blocking the afferent nociceptive input into the spinal cord and enhancing descending inhibition of nociceptive input starting in the central nervous system [9, 12–14]. This results in a decrease of the nociceptive information processing and subsequently a decrease in postoperative pain.

A theoretical advantage of opioid analgesics is that there is no analgesic ceiling. Opioids can be administered by the subcutaneous, transcutaneous, transmucosal, or intramuscular route, but the most common routes of postoperative systemic opioid analgesic administration are oral and intravenous [1, 9]. Opioids can also be administered via specific anatomic sites such as the intrathecal or epidural space, which will be described in another section of this chapter. Serum drug concentrations may exhibit wider variability, particularly in intravenous and intramuscular routes of administration [1, 9]. Generally, postoperatively opioids are administered parenterally for the treatment of moderate-to-severe postoperative pain, as these routes provide a more rapid and reliable onset of analgesic action than the oral route does. Moreover, parenteral opioid administration may be necessary in patients who are unable to tolerate oral intake postoperatively. However, in enhanced recovery pathways, the patient is allowed to restart oral intake soon after surgery, and therefore the transition from parenteral to oral administration of opioids is the next step. Furthermore, patient-controlled analgesia (PCA) has become a standard technique in the clinical treatment of acute postoperative pain [1, 9]. These PCA systems allow patients to self-administer predetermined doses of morphine and to record patient usage during the previous period in order to optimize the analgesic effects [1, 9]. A disadvantage of this method is that patients are not able to mobilize, which is the goal of enhanced recovery pathways. The most frequently used opioids in the postoperative setting are, among others, morphine and hydromorphone for parental use and oxycodone, oxymorphone, and buprenorphine for oral use [9].

Opioids in general, but also in the perioperative setting, are related to well-known undesirable side effects, such as nausea and vomiting, ileus, constipation, respiratory depression, bladder dysfunction, pruritus, sedation, addiction, and opioid-induced hyperalgesia, which may delay recovery and contribute to morbidity and mortality [15–20]. Therefore, opioids in the setting of postoperative multimodal pain management should be limited or even avoided in enhanced recovery pathways in order to improve outcomes and reduce complications and morbidity and mortality. Recently, there has been an increasing interest in trialing novel drugs such as tapentadol that are agonists of the μ(mu)-opioid receptor and as a norepinephrine reuptake inhibitor [21]. It is similar to tramadol in its dual mechanism of action, namely, its ability to activate the μ(mu)-opioid receptor and inhibit the reuptake of norepinephrine. Unlike tramadol, it has only weak effects on the reuptake of serotonin and is a significantly more potent opioid with no known active metabolites. More conclusive evidence is needed to prove its potential benefits in reducing the negative effect of opioids while maintaining a potent analgesic efficacy.

Non-opioid Analgesia

Opioids are the most commonly used drugs for postoperative pain management. However, the well-known opioid-related side effects—such as nausea, vomiting, respiratory depression, and constipation, which accompany the use of opioids—are often undesirable [9, 15–19]. Non-opioid drugs are therefore important in postoperative multimodal pain management strategies.

Acetaminophen

Acetaminophen is a basic part of postoperative multimodal pain management and used widely [1–3, 6, 9]. The precise mechanism of action remains unclear, but acetaminophen produces inhibition on the central prostaglandin synthesis and at a lesser extent on the peripheral prostaglandin synthesis [9]. Acetaminophen is analgesic and antipyretic but is not anti-inflammatory. The analgesic activity is additive to other analgesic drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids. Acetaminophen can be administered easily by oral or intravenous routes. However, as acetaminophen is associated with liver toxicity, it is recommended that the total dose should not exceed 4000 mg daily.

However, acetaminophen is probably one of the safest and most cost-effective non-opioid analgesic drug and should always be part of multimodal postoperative pain management [1, 9].

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs are a diverse group of compounds with analgesic, antipyretic, and anti-inflammatory activity. They are probably the oldest and most successful analgesic drugs known in medicine for the treatment of pain, fever, and inflammation [1, 9]. NSAIDs are also vital and key opioid-sparing components in multimodal analgesia [7, 9]. The primary mechanism of action by which NSAIDs exert their analgesic effect is through prostanoid production from arachidonic acid by either reversible or irreversible acetylation (inhibition) of cyclooxygenase (COX) enzymes. Cyclooxygenase and synthesis of prostaglandins are important mediators of peripheral sensitization and hyperalgesia. Cyclooxygenase presents in two forms: COX-1, which is necessary for normal homeostatic processes in several organs (platelet aggregation, hemostasis, and gastric mucosal protection), and COX-2, which is induced by proinflammatory stimuli and cytokines, causing fever, inflammation, and pain [1, 9, 22–24].

NSAIDs, including the available selective COX-2 inhibitors, given alone generally provide effective analgesia for mild-to-moderate pain. NSAIDs are also traditionally considered a useful adjunct to opioids for the treatment of moderate-to-severe pain. NSAIDs may be administered orally or parenterally. They are particularly useful as components of a multimodal analgesic regimen by producing analgesia through a different mechanism than that of opioids or other analgesic drug additives [1, 9, 22–24]. However, there is still debate whether NSAIDs are associated with an increased incidence of anastomotic leakage, but literature shows inconclusive evidence to avoid NSAIDs in colorectal surgery patients other than the regular contraindications [3, 25].

Perioperative use of NSAIDs is associated with potential side effects, including impaired hemostasis, worsening renal dysfunction, and gastrointestinal hemorrhage. Inhibition of COX and the formation of prostaglandins cause many of these side effects [1, 9]. Decreased hemostasis from NSAID use is due to platelet dysfunction and inhibition of thromboxane A2 (generated by COX-1), an important mediator of platelet aggregation and vasoconstriction. COX-2 drugs that do not affect platelet aggregation can be used if surgeons are concerned for bleeding [1, 9]. NSAIDs are useful as components of a multimodal analgesic strategy; however, in patients with comorbidities, evaluation should be performed regarding potential contraindications.

Gabapentinoids

Pregabalin and gabapentin are analogues of gamma-aminobutyric acid (GABA) and are anti-epileptic drugs that have gained interest for preventive analgesia in the perioperative setting. These drugs exert their analgesic effects by interaction with the α(alpha)2-δ(delta) subunit of the cellular calcium channels and inhibit calcium influx and release of neurotransmitters [1, 9]. Oral pregabalin has more bioavailability than gabapentin, but oral gabapentin improves the analgesia and reduces opioid intake and opioid-related side effects. Several studies in which the use of gabapentin was compared with placebo showed a significant reduction in morphine consumption postoperatively [1, 9]. In these studies it was also shown that the pain scores in the first 24 hours were reduced, with the greatest effect within the first hour postsurgery. These drugs may reduce the incidence of postoperative neuropathic and chronic pain. However, gabapentinoids increase the incidence of side effects such as postoperative sedation and dizziness. Gabapentinoids can be considered as part of multimodal postoperative pain management.

Ketamine

Ketamine is a well-known drug that is used as an intraoperative analgesic additive and described in Chap. 15. However, ketamine can also facilitate analgesia in the postoperative period, by attenuating central sensitization. Ketamine can be administered intravenously (bolus of patient controlled), intramuscularly, or orally [1, 2, 9, 26]. Ketamine has been shown to reduce postoperative opioid consumption and postoperative nausea and vomiting (PONV) [1, 2, 9, 26].

A potential concern is the impact of ketamine on the cognitive level of patients with the use of perioperative ketamine infusions. However, these effects are rarely seen for analgesic doses [1, 9]. Ketamine can be considered as part of multimodal approach to postoperative pain management.

Tramadol

Tramadol is a weak synthetic opioid, acting centrally on the μ(mu)-receptor and thereby inhibiting the reuptake of serotonin and norepinephrine [1, 9]. Tramadol is effective in treating mild-to-moderate postoperative pain. The analgesic effects are comparable to those of ibuprofen, codeine, and aspirin [1, 9]. Combinations of tramadol with drugs such as acetaminophen and NSAIDs are effective and reduce the incidence of tramadol-induced side effects. Tramadol can be administered intravenously (PCA) and results in similar pain scores when compared with that from intravenous PCA

opioids. Tramadol for postoperative analgesia shows some advantages compared with opioids: a relative lack of respiratory depression, major organ toxicity, depression of gastrointestinal motility, and a low risk for abuse [1, 9]. However, tramadol also has some undesired side effects (up to 6%), such as dizziness, drowsiness, sweating, nausea, vomiting, dry mouth, and headache [1, 9]. Tramadol can be used in multimodal postoperative pain management but may not be the first-choice drug.

Epidural Analgesia

Analgesia provided by an indwelling epidural catheter is a safe and effective technique for management of acute postoperative pain [1, 3, 9]. However, epidural analgesia incorporates a wide range of options in terms of the choice of drugs (opioids and additives) administered and the level of epidural catheter placement, onset, and duration of the perioperative use. Opioids have routinely been used to control postoperative pain mainly in the intravenous route. However, opioids either as single injection or continuous infusion are effective in controlling postoperative pain and regarded as superior to that with systemic opioids alone [3]. Although postoperative epidural analgesia has been the gold standard in open thoracic and abdominal surgery, epidural analgesia is nowadays not recommended in laparoscopic procedures within enhanced recovery after surgery pathways anymore [3]. However, in other surgical specialties, epidural analgesia deserves a place in the management of postoperative pain, which is described in the many different enhanced recovery after surgery protocols published.

Opioids administered in the epidural space, either alone or in combination with local anesthetics, provide analgesia via the cerebrospinal fluid and via supraspinal or systemic analgesia [1, 9]. Opioids diffuse through the spinal meninges into the cerebrospinal fluid and produce analgesia on the spinal level. Opioids bind to spinal opioid receptors located at specific areas in the dorsal horn of the spinal cord, and these locations provide the basis for selective opioid analgesia in the cerebrospinal fluid. Opioids may also be absorbed into the plasma and redistributed to the brain stem via the bloodstream and produce analgesia on the supraspinal level [1, 9].

In common practice, postoperative continuous epidural infusions of opioids are combined with the administration of local anesthetic drugs. The combination of opioids with local anesthetics is more effective in analgesia than opioids alone [27, 28]. The exact location and mechanism of action of epidural-administered local anesthetics remain unclear. However, potential sites of action include spinal nerve routes, dorsal root ganglion, or the spinal cord [9].

Thoracic epidural analgesia (at level T7–T10) remains the gold standard in patients undergoing open colorectal and thoracic surgery. Several randomized controlled trials and meta-analyses have demonstrated superior analgesia compared with patients receiving systemic opioids. Lumbar epidural blockade is not recommended, as this results in an insufficient upper sensory block covering the surgical incision, lack of blockade of sympathetic fibers, and risk of lower limb motor block and urinary retention [29]. These benefits of epidural analgesia have not been demonstrated in patients undergoing laparoscopic colorectal surgery, and epidural analgesia results even in increased LOS in patients undergoing minimally invasive surgery [30]. Moreover, using multimodal analgesia techniques, such as intravenous lidocaine, spinal analgesia, abdominal trunk blocks, intraperitoneal local anesthetic, or continuous wound infusion of local anesthetics, has been shown to provide adequate analgesia, similar to those obtained with epidural analgesia [31]. Additional epidural analgesia might still be valuable in patients with chronic pain, in patients in whom the conversion rate to open surgery is high, or in other surgery subspecialties as described in the enhanced recovery after surgery pathways protocols [3, 9].

Because of its preemptive analgesic effect, epidural analgesia should be initiated before the start of surgery and continued in the intraoperative and postoperative period up to a maximal 72 hours, depending on the local agreement of the protocol.

A disadvantage of the use of thoracic epidural analgesia is the primary epidural failure rates that continue to remain high in some reports (ranging between 22% and 32%). Additional methods to correctly identify the epidural space (i.e., epidural stimulation or wave form analysis) and increase the success rate of epidural blocks can be employed [32, 33].

Besides pain control, it is well established that epidural blockade with local anesthetics, initiated before and continued during and after surgery, is a successful technique to minimize the neuroendocrine and catabolic response to surgery [29]. Epidural blockade leads to blockage of surgical stress, resulting in attenuation of insulin resistance and minimizing postoperative protein breakdown, which is important as together with early feeding the nitrogen balance is normalized and protein synthesis facilitated [3] However, these data on metabolic effects have been mainly shown for open surgery, and data for laparoscopic surgery are yet to be found.

The choice of opioid varies, but in clinical practice lipophilic opioids (e.g., fentanyl, sufentanil) are preferred in order to allow rapid titration of analgesia. Use of hydrophilic opioids (morphine and diamorphine) as part of a local anesthetic–opioid epidural analgesic regimen may also provide effective postoperative analgesia but is mainly used as the opioid of choice for spinal administration. The choice of local anesthetic for continuous epidural infusion also varies. In general, bupivacaine, ropivacaine, or levobupivacaine are chosen because of the differential and preferential clinical

sensory blockade with minimal impairment of motor function. The optimal local anesthetic and opioid dose that provides the lowest pain scores with the fewest medication-related side effects is unknown, and further investigation is needed to determine this optimal dose. The addition of adjuvant drugs such as alpha2-adrenergic agonists (clonidine or dexmedetomidine) or N-methyl-D-aspartate (NMDA) antagonists (ketamine) has been suggested to enhance analgesia while minimizing opioid side effects [9]. However, additional safety and analgesic data are needed.

Side effects related to the use of epidural analgesia are the typical side effects seen after the administration of systemic opioids: respiratory depression (incidence 0.1–0.9%), nausea and vomiting (incidence 45–80%), pruritus (incidence up to 60%), and urinary retention (incidence 70–80%). Furthermore, a disadvantage of this invasive technique is the primary failure rates that continue to remain high in literature (22–32%). Additional methods to correctly identify the epidural space (epidural stimulation or wave form analysis) and increase the success rate of epidural blocks can be employed [1–3, 9].

The use of epidural analgesia in enhanced recovery after surgery pathways may also contribute to improved non-analgesic outcome. Several publications have shown benefits including acceleration of the recovery of bowel function after colorectal surgery [34–36] and reduction of the risk of respiratory [36, 37] and cardiovascular complications [36]. To the contrary, postoperative arterial hypotension, urinary retention, and motor blockade may require additional postoperative care and delay hospital discharge [36]. The impact of epidural analgesia on colorectal cancer recurrence and metastasis [38, 39] remains to be investigated further, especially in the context of an ERAS program.

Spinal Analgesia

As part of postoperative multimodal pain management, spinal analgesia can be used as an adjunct for general anesthesia in laparoscopic procedures. The efficacy of spinal anesthesia/analgesia is high, and this technique has a relatively low complication profile [40]. Opioid receptors exist in specific areas in the dorsal horn of the spinal cord, and these locations provide the basis for selective opioid analgesia in the cerebrospinal fluid. Intrathecal opioids are blocking the transmission of substance *P*, a process that is mediated by gamma-aminobutyric acid presynaptically and by glycine postsynaptically. Spinal analgesia has been used in enhanced recovery after surgery protocols in order to facilitate fast recovery after laparoscopic colorectal surgery by minimizing opioid consumption [9, 41]. When compared with epidural anesthesia, the patient can be mobilized sooner and is at less risk of hypotension and fluid overload, which results from the sympathetic block induced by continuous thoracic epidural analgesia and is frequently seen [30]. Spinal analgesia can be applied with a combination of local anesthetic such as bupivacaine (0.5%) and long-acting opioids (morphine or diamorphine) and is used with the total volume dosing of no more than 2.0 ml to avoid high spinal block. Furthermore, in addition to the local anesthetic effect, spinal analgesia techniques have been shown to reduce the endocrine-metabolic stress response but only for the duration of action of the local anesthetic whereafter it returns to levels of controls [42]. The addition of a long-acting opioid has the benefit of reducing morphine requirements postoperatively by up to sixfold, with the ability to mobilize patients immediately after surgery once the motor block has worn off [43]. Although recovery was earlier in patients using morphine alone, no benefits have been shown regarding length of hospital stay [43].

Numerous studies have been published that have used other adjuncts in combination with opioids and with or without local anesthetics in order to improve analgesia while minimizing the effects of intrathecal opioids. Alpha2-adrenergic agonists such as clonidine or dexmedetomidine may increase the antinociceptive threshold by activating descending noradrenergic pathways in the spinal cord [3, 9]. However, no conclusive data have been published regarding these adjuncts in enhanced recovery pathways.

The recommended doses used are lower than the commonly used doses in clinical practice: 100–150 μ(mu)g of morphine or 300–500 mcg of diamorphine [9]. The main concern of using intrathecal opioids is that the incidence of (delayed) respiratory depression is no greater than when given by other routes [9]. Therefore, frequent monitoring of vital signs in patients who have received intrathecal opioids is recommended. Furthermore, patients should be assessed for other adverse reactions such as nausea, vomiting, pruritus, urinary retention, and sedation of intrathecal opioids [1, 9]. These side effects can be easily treated with the currently available pharmacological drugs. Intrathecal opioids have been shown to be safe and effective in postoperative pain management.

Surgical Site Infiltration and Locoregional Techniques

As the role of epidural analgesia within the setting of enhanced recovery pathways has been questioned, especially with regard to laparoscopic operations, alternatives are discussed [29, 31, 44–47]. Some of these possible alternatives are local anesthetic wound infiltration and local anesthetic abdominal wall blocks, as a component of multimodal analgesia [31, 44–46].

Surgical site infiltration technique for the abdominal wall would consist of the administration of local anesthetic into

the peritoneal, musculofascial, and subdermal tissue planes at closure of the surgical wound. However, ideally, cutaneous and subcutaneous infiltration with local anesthetics should be performed preincision for preventive analgesia. Infiltration of the fascial plane with local anesthetic infusion through catheters has been reported to improve pain relief, reduce opioid requirements, and improve postoperative outcome [4, 20, 22, 31]. The subdermal tissue can be infiltrated to block the nociceptive input from the peripheral nerve endings. In open abdominal hysterectomy through a horizontal incision, it was found that surgical site infiltration (peritoneal, musculofascial, and subdermal planes) provided superior postoperative analgesia compared to bilateral transversus abdominis plane blocks [27, 31]. Surgical site infiltration or more specific port-site local infiltration with local anesthetics does appear to reduce postoperative pain compared with placebo. However, as limited data are available, further well-designed studies are necessary to assess the analgesic efficacy of the proposed infiltration technique.

Locoregional techniques for abdominal surgery such as transversus abdominis plane (TAP) blocks are the most widely studied (see Chap. 16). TAP blocks were first described in 2001 as the classic landmark-based technique, but since then multiple variations have been described, including two-point, four-point, ultrasound-guided, and laparoscopic-visualized blocks. TAP blocks provide adequate pain relief to the anterior abdominal wall from T10 to L1 and have been clearly demonstrated to provide an opioid-sparing approach in colorectal surgery [48, 49]. As TAP blocks only provide analgesia reliably below the umbilicus, subcostal and rectus blocks are to be added in order to cover the upper abdomen.

Initial studies up to early 2016 on TAP blocks found no comparisons with other methods of analgesia and limited evidence of reduced opioid use [50]. More recent studies indicated the benefits of TAP blocks in abdominal surgery in multiple specialties including gynecologic, general, bariatric, transplant, [51–55], and colorectal surgery with less postoperative opioid consumption and faster recovery of the gastrointestinal tract function and patient recovery [56, 57]. Drawback of abdominal blocks is the short duration as bupivacaine and ropivacaine used in traditional TAP blocks have a short half-life (8–10 hours) [58], and therefore infusion catheters can be used to prolong the duration [55]. As part of postoperative multimodal pain management, surgical site infiltration and abdominal wall blocks can be used.

Conclusion

Postoperative analgesia resulting in adequate pain control is essential in enhanced recovery pathways. Opioid avoiding or sparing techniques in most types of surgery are associated with early mobilization, fast return of bowel function, fewer complications, and a reduction in LOS. Therefore, the key is to avoid opioids when possible and apply multimodal analgesia in combination with spinal/epidural analgesia (in open surgery) when indicated. The benefit of using a multimodal approach to postoperative pain management is based on the concept that several multiple pain-reducing mechanisms will improve pain control while avoiding the side effects of each drug.

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Nursing Considerations During Patient Recovery

25

Basile Pache, Valérie Addor, and Martin Hübner

Introduction

The patient is in the center of the enhanced recovery after surgery (ERAS) care. The nursing team working bedside plays a crucial role in the implementation of the enhanced recovery program and maintaining daily ERAS routines.

The aim of this chapter is to summarize the current evidence on the important role of nursing in ERAS care and to describe the different facets of perioperative nursing. Previous chapters have covered the role of ERAS nurses in preoperative patient education and nutrition. Therefore, emphasis in this chapter is on nursing at the surgical ward.

Current Evidence

The unique function of the nurse is to assist the individual, sick or well, in the performance of those activities contributing to health or its recovery, as written by Henderson [1]. Nurses are in a privileged position to be the frontline healthcare providers.

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What Makes the Difference with Standard Care? – A Shift of Activities!

In the traditional care scheme, the patient was prepared for digestive surgery with oral bowel cleansing, fasting, and preoperative sedation. In the postoperative period, most patients were kept bedbound for up to a week. The main nursing tasks included feeding, administration of medications, and management of catheters, drains, intravenous infusions, and nasogastric tubes. Oral nutrition was started only after signs of bowel recovery (first stool/flatus), typically 3–5 days after surgery.

Within ERAS care, the typical patient is mobilized and starts on oral intake, often within a few hours after surgery. This paradigm shift involves increasing the range of responsibilities for the nurse to include not just traditional care but also educational, motivational, and various monitoring activities.

It is of particular importance that nurses are made aware of their role in the ERAS care pathway, since compliance with ERAS care elements is closely associated with improved clinical outcome [2]. Therefore, education of the nursing staff is crucial for successful implementation of ERAS. Explanation of the process, with a proof of outcomes of the institutional results by regular feedback, can convince even staff members who may be reluctant to change about the potential impact and benefits of ERAS. In a study by Roulin et al., nurses were less reluctant to change practice following ERAS implementation compared to surgeons [3]. Furthermore, by having the nurses "on board," continuity of care was maintained also during the weekends, when often weekday routines otherwise fail [4].

Beyond the basic ERAS knowledge and skills, specific knowledge of ERAS-related nursing has to be acquired [5], and a protocol alone is not enough to successfully implement an ERAS program, as shown by Maessen et al. [6] Unfortunately, there are only a few studies assessing

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specifically the effects of nursing in ERAS care. Published evidence is mostly based on focus groups and qualitative surveys [7–11].

An effective postoperative management starts with an efficient preoperative patient education. The main aim of this education is the empowerment of the patient. Intensive preoperative preparation has been shown to have a number of benefits, including reduced postoperative pain and anxiety, increased knowledge of self-care and management of complications, and reduced hospital stay [12–14]. A qualitative investigation exploring experience and opinions of caregivers stressed the importance of good interdisciplinary collaboration [15].

Clinical Pathways

The transfer from guidelines to practice can be facilitated by employing standardized patient pathways—so-called clinical pathways. They provide a structured framework for the care processes in the busy day-to-day practice and help reduce variability and redundancy in clinical care for all caregivers including nurses, surgeons, and anesthesiologists. This is of particular importance in teaching institutions with frequent staff changes and a high number of inexperienced junior staff rotating through as part of their training. Clinical pathways are a "working canvas" that sometimes needs to be adjusted to the patient's condition [3]. Planned patient pathways have shown to reduce morbidity, complications, and costs [16].

Reasons for Non-compliance with the Protocols

The success of ERAS protocols relies on the actual application of the pathway as a whole [2] and not only for some selected items [17]. Non-compliance is therefore a constant concern and may have several reasons. In a study conducted by Roulin et al. [3], the nurses were responsible for causing 14% of the deviations in compliance with individual care items. Surgeons and anesthetists were responsible for 21% and 34% of the deviations for non-compliance, respectively. However, 78% of these deviations were classified as medically justified.

Despite the fact that most of the important items (mobilization, weighing, nutrition, education) are prescribed or requested by medical staff, the application of such items relies upon the nurses in day-to-day practice. It is always useful to audit these processes to help implementation but also sustainability of improvements. There are several ways to audit (as described elsewhere). The ERAS® Society has developed the ERAS Interactive Audit System (EIAS) to complement and mirror the guidelines that the Society develops and updates. This system captures process measures and outcomes so they can be audited together.

Nursing Workload

ERAS care can be demanding and involves new care items for the nursing staff [18]. Interestingly, nursing time spent per patient and day was shorter for ERAS patients in one study (Fig. 25.1) [19]. This can be explained by the fact that many of the traditional nursing work chores have become partially obsolete for ERAS patients who take a more active part in their recovery process and thereby gain independence much faster than they used to do. Early concerns that the additional activities associated with enhanced recovery pathways would increase the workload for nurses have not been demonstrated to be true in the literature [20]. Another concern that early discharge with ERAS may impact negatively on patient's satisfaction and views about nursing care could not be confirmed [21]. A cohort study in colorectal surgery measured a decrease in nursing workload with implementation of ERAS [19]. Interestingly, it also showed that an increased compliance with ERAS protocol was significantly correlated with decreased nursing workload. This can be explained by optimization and standardization of postoperative care. A study specifically focused on workload and ward environment of a gynecology unit showed a reduction in total time used in nursing activities per stay compared to prior to ERAS implementation [22]. Another gynecology study showed that due to shorter hospital stay, perioperative counseling and education—although it was recognized as a key element—might be neglected due to the short time of hospitalization [23].

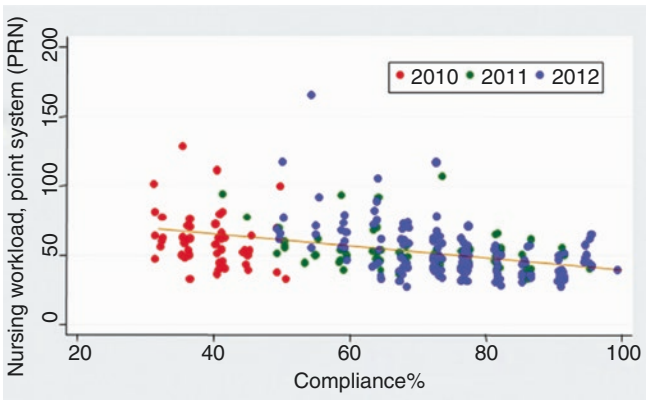

Fig. 25.1 Correlation of nursing workload with the compliance with ERAS protocol. Nurse's workload is inversely correlated to compliance with the ERAS protocol on a linear fashion. (Reprinted with permission from Hubner et al. [19])

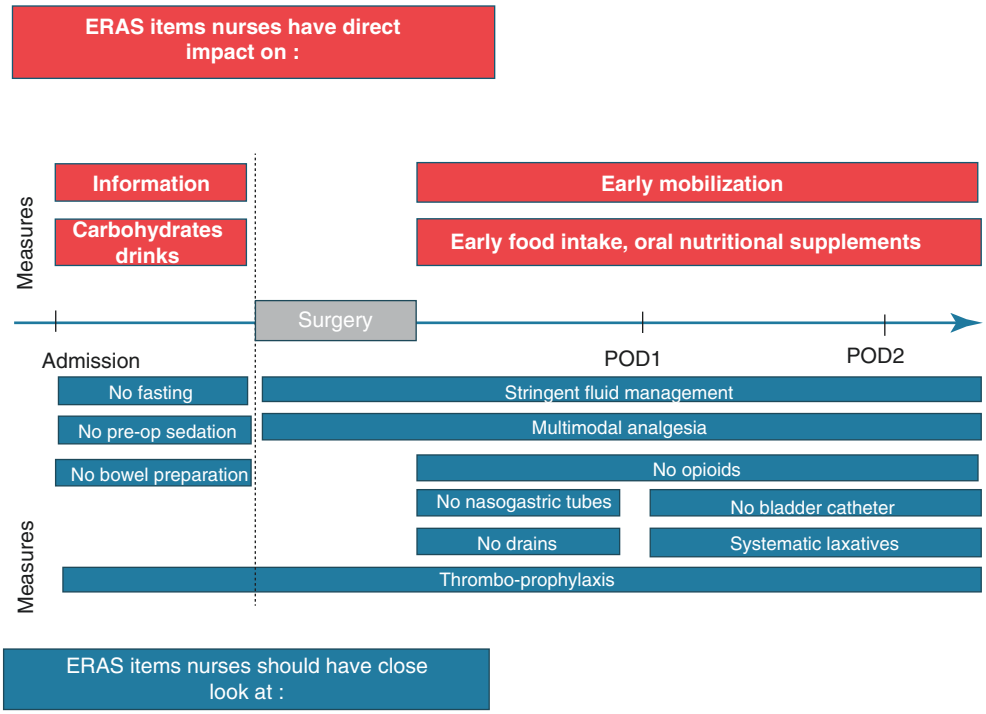

Fig. 25.2 Nurses' involvement in ERAS perioperative items. In red, ERAS items nurses have major impact on. In blue, ERAS items performed by nurses under medical order

Nurses on the Surgical Ward

The specific roles of nurses within ERAS care are summarized in Fig. 25.2.

ERAS items related to the nurse's role in preoperative care are summarized below. These include:

- Preoperative nutrition: In order to decrease insulin resistance and its negative impact, carbohydrate loading is recommended the evening prior to surgery and again 2 hours before surgery. Nurses should pay particular attention and give enough information to the patient in order to understand the importance of the carbohydrate drinks. Furthermore, correct timing and good planning are crucial, especially for patients not being operated as the first patient on the list.
- Time can be gained by omission of typical care items within traditional care schemes. One example is oral bowel preparation, which also causes dehydration that may affect anesthesia management during surgery and also recovery after surgery [24]. Similarly, traditional preoperative long-acting sedative preoperative medication may also delay postoperative recovery [25].
- Thrombo-prophylaxis with low-molecular-weight heparin (LMWH) together with sequential compression devices and mobilization should be started already in the preoperative setting.
- A reminder of the postoperative recovery process is useful to complement prior detailed information provided by the dedicated ERAS nurse.

ERAS items related to the nurse's role in postoperative care include some of the following:

- Nurses are often the frontline providers to assess and diagnose fluid overload by monitoring patient weight development and bringing this to the attention of the medical staff. Skilled nurses are able to minimize patient harm by reducing fluid overload, limit unnecessary intravenous fluid administration, and encourage patients to resume oral fluid and diet intake shortly after surgery.
- Nurses are also actively involved to ensuring efficient and timely pain management. It is important for nurses to be aware of the advantages of good pain management in improving many aspects of the patient's care, such as early mobilization, respiratory physiotherapy, early intake of food and drinks, and overall well-being [26]. The nurse should proactively and regularly assess pain and act accordingly.
- Postoperative nausea and vomiting (PONV) has been reported to occur in up to 27% of patients [27, 28]. Routine PONV prophylaxis should be standard of care. Careful attention by the nurse is therefore mandatory to administer the medications according to the patient care

pathway. Additional medications might need to be provided on demand if prophylaxis is insufficient. Opioids should be avoided or minimized, due to their side effects causing nausea and vomiting and their potential impact disturbing bowel function. Mobilization stimulates gut motility and relieves symptoms of nausea and vomiting. Chewing gum has been proven to provide some beneficial effect on return of gut motility and should therefore be made accessible to the patient [29].

- Bed rest and postoperative pain are major sources of pulmonary complications. They both induce reduced ventilation, with atelectasis and subsequent potential pulmonary superinfection. Nurses must encourage early mobilization and teach patients how to use incentive spirometry, although its usefulness is still debated.
- Patient mobilization is a cornerstone of ERAS care. It does require full participation from the patient, not just from the nurses and the nurse's aides. The ERAS guidelines suggest getting the patient out of bed on the day of surgery. On postoperative day 1, the patient should be encouraged to stand up and walk and spend at least 4–6 hours out of bed. Patients should be encouraged to have their meals served out of bed sitting on a chair at the table or in a dedicated dining room in order to promote mobilization.
- Weight measurement sometimes remains one of the most difficult goals to achieve in ERAS. The reasons are multiple. Sometimes it may be lack of motivation and information on the importance to monitor such data and training of nursing staff when patients are in ancillary units.

ERAS-Specific Education

Education is an important part of nursing within ERAS care. Information does not only concern the care pathway but should also cover discharge planning and set expectations for recovery. The clinical nurse specialist (CNS) role is expanding across various specialties, as summarized below.

- Colorectal surgery: In addition to the holistic management of cancer patients by the CNS, a patient undergoing colorectal surgery with a probability of stoma creation should have the benefit of preoperative education from dedicated stoma nurses. Postoperatively, stoma nurses will work together with the other ward nurses to ensure the patient correctly manages the stoma during their hospital stay and reaches a level of confidence in managing it prior to discharge.
- Gynecology: Assessment of self-perception and psychological impact after surgeries that often involve removing organs related to womanhood.
- Head and neck surgery or breast reconstruction: Flap monitoring [30, 31].
- Liver, pancreatic, and stomach surgery: Postoperative glycemic control [32].
- Esophagectomy and gastrectomy: The CNS plays an important role in the management of upper gastrointestinal surgery patients. They are the contact access to patients prior to admission, and they visit patients during their hospital stay. Nurses at the ward ensure that patients receive multiple small meals, with cautious increase in food intakes according to tolerance [33, 34].

Of note, sometimes it can be challenging to find the equilibrium between providing all essential information on one hand and avoiding overwhelming the patient with too much information on the other hand. This may be counterproductive for the patient's comprehension of specific items [35]. Nursing assistants may also contribute to communicating recommendations and helping with prescribed therapies in the daily practice and can help encourage patient mobilization, fluid intake, and daily weight monitoring—emphasizing a multidisciplinary approach to ERAS care.

Discharge Planning

Since time to discharge is usually reduced with ERAS, nurses should ensure the patient is ready for early discharge. Nurses are often asked to provide an assessment of the patients' ability to take care of themselves prior to leaving hospital. Together with the patient, they shall explore the pitfalls that may arise after the return to normal life.

Patient must meet certain discharge criteria before being allowed to leave the hospital. Medical discharge criteria include sufficient oral intake, adequate pain control (on oral medications), and adequate mobilization level. Bowel recovery is no longer a mandatory requirement for safe discharge [36].

The nurse, case manager, and other members of the care team need to ensure that the patient has hospital contact information in case of an emergency or if questions related to their surgery and follow-up arise after discharge. The patient should have adequate information and understanding of (1) pain management; (2) nutrition; (3) how to deal with nausea/vomiting; (4) bowel movement, diarrhea and constipation; (5) wound management; and (6) information about going back to work, returning to physical activities, restarting home medication, and the ability to drive and travel.

Nurses play an important role in the follow-up after discharge. In many hospitals, there is a nurse-led telephone follow-up service that helps maintain contact with recently discharged patients. A study of more than 200 patients within 4 weeks of discharge from the hospital showed that despite a quicker return home, the majority of patients were coping

well and many of the concerns reported were easily addressed over the telephone [37]. Therefore, it is crucial that patients and their families are aware that they will have access to the members of their healthcare team, especially when they are discharged early from the hospital.

A study assessing effect of communicated discharge information on surgical patients found that those who received information preoperatively were less likely to access a health facility than those who had not. This could lead to less unnecessary utilization of healthcare resources and greater patient satisfaction. Smartphone and other electronic applications are a popular new way of communicating with patients before and after hospitalization. The impact of these new communication techniques is currently being investigated.

Future and Development

Nurses will remain key players in ERAS care. ERAS sustainability over time will rely on various key factors. Positive feedback to the nurse's team will enhance team building and enhance compliance with ERAS protocols [38].

It is also important to audit nurses' performance and help them improve their roles as frontline healthcare providers constantly interfacing with patients. This will hopefully lead to better compliance and better data collection.

ERAS teaching should be an integral part of the nursing undergraduate curriculum. On surgical wards, nurses should be familiarized with various ERAS guidelines, evidence supporting clinical practices, and implementation initiatives.

Conclusion

Nurses are important members of the team taking care of the surgical patient. They can help ensure compliance with ERAS pathways, participate in patient-centered care, and help coordinate care among the different members of the team. Continuous education of nurses in all aspects of surgical care and ERAS is critical to the overall goals of quick patient recovery.

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Part V

Prevention of Postoperative Complications

Long-Term Outcomes Related to ERAS

26

Ismail Gögenur and Rasmus Peuliche Vogelsang

Introduction

The vast majority of literature concerning enhanced recovery after surgery (ERAS) focuses on short-term outcomes after surgery. Fewer studies describe intermediate outcomes such as recovery after discharge, and very few publications report the long-term effects of ERAS on patient-related outcomes such as quality of life, organ-specific quality of life, and—in patients undergoing cancer surgery—oncological outcomes. A major part of the literature concerning ERAS has been in patients undergoing cancer surgery. The potential drivers in the perioperative period that affect the possibility of having adjuvant oncological treatment and long-term poorer oncological outcomes are not described in detail in the literature. It has been shown that some elements of the perioperative pathway, including the surgical approach and anesthetic care, may in fact have a substantial impact on long-term oncological and other recovery-related outcomes [1–3].

In most specialties where surgery is performed in a patient with cancer, there are no radiological or biochemical signs of residual disease after the primary removal of the tumor. Although this is the case, one out of three patients will, depending on the primary tumor, have recurrence within a few years [4]. This is obviously due to residual micrometastatic disease [5]. Recent studies indicate that even brief exposure, such as the choice of the anesthetic method during surgery (inhalational anesthesia vs. total intravenous anesthesia), may have an effect on both long-term oncological and overall survival [6, 7]. It has been long known that the occurrence of perioperative events, such as receiving a blood transfusion or having an infectious episode in the postoperative period, renders the patient to high risk of recurrence [8–10]. The key drivers behind this are believed to be suppression of the adaptive immune system and production of systemic and local prometastatic factors in the days after surgery. Thus, elements of the surgical stress response—release of pro-inflammatory mediators such as interleukin (IL)-6, tumor necrosis factor (TNF)-alpha, vascular endothelial growth factor (VEGF), and matrix metallopeptidase (MMP)-9—will result in a prometastatic phenotype [11]. There is a clear dose-response relationship with respect to the risk of having a poorer oncological outcome. The lowest risk is in the patient undergoing minimally invasive surgery without postoperative complications. The highest risk is in the patient undergoing major open surgery, suffering from postoperative infectious complications, and having reoperations [12, 13]. Studies have also confirmed that across surgical disciplines, there is a significant impact on overall survival whether a patient suffers from a postoperative complication or not [14, 15].

As the individual components of ERAS as well as the general implementation of ERAS lead to fewer infectious and overall complications [16], ERAS may result in improved oncological outcomes. The focus of this chapter is to present the literature describing the important components within the implementation of a full ERAS protocol and the individual components of ERAS on long-term patient outcomes with special emphasis on long-term oncological outcomes.

The Association Between the Surgical Stress Response and Long-Term Oncological Outcomes

The surgical stress response includes a complex pattern of changes all directed toward repair and recovery after the surgical trauma. In recent years, it has been suggested that the

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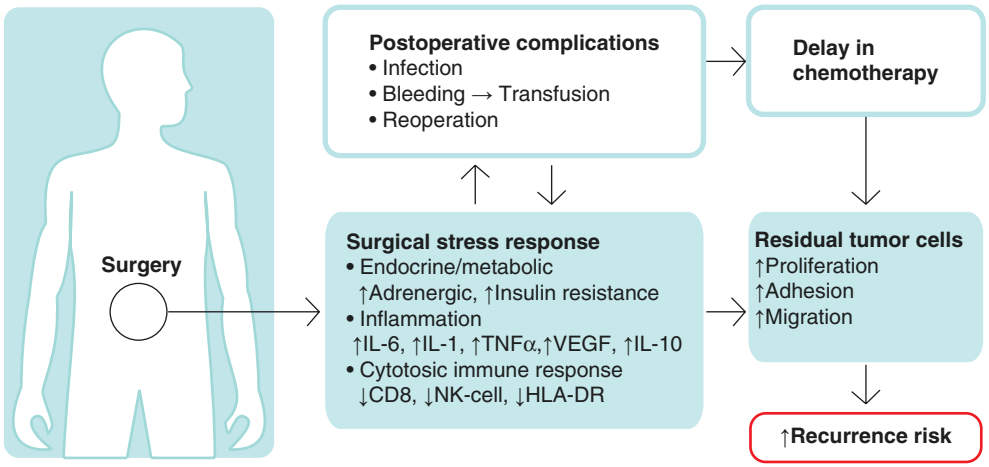

Fig. 26.1 The effects of surgery and perioperative stress on cancer recurrence. Abbreviations: IL-6 interleukin 6, IL-1 interleukin 1, TNFα (alpha) tumor necrosis factor alpha, VEGF vascular endothelial growth factor, IL-10 interleukin 10, CD8 cluster of differentiation 8, NK cell natural killer cell, HLA-DR human leukocyte antigen DR subtype

surgical stress response in patients undergoing oncological surgery may lead to a series of endocrine, metabolic, inflammatory, and immunological changes that may have an effect on long-term oncological outcomes [5, 11] (Fig. 26.1).

The development of cancer is the result of a series of genetic mutations, and the metastatic process is a late occurring event where a complementary cascade of genetic changes enables the tumor cells to disseminate from the primary tumor [17, 18]. Subsequent entry into the vascular or lymphatic circulatory system, survival in the circulation, adherence to a pre-metastatic niche, and establishment of malignant growth at a distant site is the result of subsequent mutational changes. The exposure of factors that may stimulate the metastatic process of tumor cells located in the systemic and/or lymphatic vasculature, or at other distant sites, may render the patient susceptible to the development of clinical metastases. The surgical stress response includes several of these stimulatory factors, and there is apparently a dose-response relationship, with increased surgical stress response leading to a higher risk of a prometastatic phenotype [5, 11]. One of the pioneering studies within this field was by Tsuchiya et al. who demonstrated this in an experimental study including colon cancer cells injected into mice in relation to different levels of surgical stress [19]. Mice were injected with colon cancer cells, and the outcomes of interest were systemic stress response markers such as IL-6 and microscopically evaluated pulmonary metastases. The mice were divided into five groups: (1) untreated controls; (2) mice only exposed to anesthesia; (3) mice undergoing laparotomy, (4) laparotomy and appendectomy; and finally (5) laparotomy, appendectomy, and left hepatic lobectomy. The authors showed that there was a clear relationship between the enhancements of metastases in proportion to the increase in surgical stress. The metastatic enhancement was dependent on the levels of matrix metalloproteinases. Several other studies have demonstrated this association in different experimental models and different cancers [20–24].

One of the important factors ensuring metastatic growth is perfusion to the metastatic niche. This is stimulated by tumor cells secreting vascular endothelial growth factor. Several studies in humans undergoing cancer surgery have shown an increase in VEGF in the postoperative period [25–27]. This is an essential process in wound healing. The secretion of VEGF is dependent on the magnitude of surgery, as shown in several clinical studies including randomized clinical trials (RCTs) where open surgery results in higher postoperative VEGF values when compared with the corresponding laparoscopic procedure [28]. It is hypothesized that this may translate into improved long-term oncological outcomes. Meta-analyses of RCTs have not shown an overall survival benefit in patients undergoing laparoscopic colon cancer surgery compared with the corresponding open procedure [29]. However, a positive/preventive effect has been shown in a few studies [30, 31]. In an RCT by Lacy and colleagues, a survival benefit was proven in the subgroup of patients with stage III colon cancer undergoing laparoscopic surgery compared with the patients undergoing open surgery [32].

A hypothesis could, therefore, be that by reducing the surgical trauma through minimally invasive surgery in an ERAS setting, the prometastatic milieu in the postoperative period may be abolished. However, in a recent trial including six patients undergoing minimally invasive surgery for colon cancer in an ERAS setting, it was shown that this was not the case [33]. The authors performed whole blood transcriptional profiling including more than 30,000 genes at 5 time points in the perioperative period and demonstrated that there was a substantial suppression of the adaptive immune system, which is necessary for cytotoxic activity toward tumor cells, and at the same time there was a massive upregulation of genes involved in the prometastatic process [33]. Apparently, even in state-of-the-art minimally invasive surgery and ERAS, there may still be a promotion of the metastatic process and immune suppression, potentially leading to increased risk of metastases.

Overall Effect of ERAS on Oncological Outcomes

In this section, we will examine the long-term oncological benefits of ERAS adherence and potential benefits based on reduced overall complication rates.

Long-Term Oncological Benefits of ERAS Adherence

A major discussion is concerned with what are the key elements of ERAS and how should adherence to ERAS be evaluated [34]. This is described in detail elsewhere in the book. One approach to this has been by Gustafsson et al. [35] who investigated how the adherence of certain elements of ERAS in the preoperative and intraoperative periods was associated with long-term oncological outcomes. In more than 900 patients, the authors investigated the impact of compliance with ERAS protocols on short-term outcomes. They showed that adherence to ERAS for more than 70% of the key elements investigated was associated with shorter hospital length of stay (LOS) and reduced postoperative symptoms and complications [35]. The number of patients having complications in the low adherence group was 42% compared with 31.5% in the high adherence group. It was also demonstrated that adherence to preoperative and intraoperative ERAS elements was associated with improved inflammatory stress response demonstrated by C-reactive protein (CRP) concentrations. In the follow-up paper, the author group investigated the impact of ERAS adherence on long-term oncological outcomes and demonstrated a dramatic effect on cancer-specific mortality [3]. A high adherence to ERAS (>70%) resulted in an 85.4% colorectal cancer (CRC)-specific 5-year survival compared with 78.7% in the low adherence group [3]. Other studies have shown similar effects on immediate postoperative outcomes after cancer surgery, although without long-term oncological follow-up [36, 37].

In a study by Arrick et al., 12 components of ERAS were examined in 495 consecutive major colorectal surgical patients compared with a pre-ERAS cohort of 99 patients. It was shown that in the group of patients with more than 75% process adherence, there was a significant reduction in the complication rate and mean LOS [36].

Benefits Based on Reduced Overall Complications

The primary underlying hypothesis concerning the positive effects of ERAS on long-term oncological outcomes is based on the benefits of associated outcomes in the short-term period after surgery. It is believed that the ERAS-associated reduced complication rate may be the primary driver. However, there are also studies confirming that ERAS by itself, when added to minimally invasive surgery, may result in improved immune functions in the postoperative period. Thus, in the LAFA-trial (LAparoscopy and/or FAst track multimodal management versus standard care), this was specifically examined in patients undergoing non-metastasized colon cancer surgery [38, 39]. Biomarkers indicating level of immune response—systemic human leukocyte antigen-DR isotype (HLA-DR) expression, CRP, and IL-6—were examined 1, 2, 24, and 72 hours after surgery. This was a four-arm RCT including patients undergoing laparoscopic or open surgery with or without ERAS. It was shown that the immune function demonstrated by the HLA-DR in patients undergoing laparoscopic surgery with ERAS was the highest compared with the other groups, indicating a preserved cellular immune response [39].

As previously mentioned, one of the primary drivers of improved oncological outcomes after surgery in an ERAS setting may be due to reduced postoperative complications. Recently an important outcome was introduced in the measurement of quality of perioperative care in patients undergoing oncological surgery. This is the so-called RIOT concept, which indicates the return to intended oncological therapy [1]. This quality metric is a novel and very useful metric as it encompasses an important outcome that can be directly related to surgical and perioperative care. The concept includes two components, with one component representing whether the patient did or did not start intended oncological therapy after surgery and the second being the time between surgery and initiation of oncological therapy (Fig. 26.2).

There is an obvious survival benefit for patients receiving adjuvant chemotherapy, making the first component of RIOT clinically relevant. The second component indicating time to chemotherapy is meaningful as there are several publications demonstrating that long-term oncological outcomes improve as the time to chemotherapy is reduced. In a pioneering study within this field, Aloia and coworkers investigated RIOT in patients undergoing surgery for colorectal hepatic metastases [1]. They identified a baseline RIOT rate of 75% with a median RIOT time of 42 days. After implementing an ERAS pathway (including minimally invasive surgery), there was a dramatic increase in the RIOT rate to 95% [1].

As stated previously, there is a clear dose-response relationship between the severity of postoperative complications and the disease-free survival, recurrence rate, and overall survival after oncological surgery. In a publication from Delaney and coworkers from the Cleveland Clinic in the United States, this was demonstrated in a cohort of patients undergoing colorectal cancer surgery in an ERAS setting. The authors showed that any postoperative complication reduced overall survival (66% vs. 77%), disease-free survival (53% vs. 70%), and cancer-specific survival (81% vs.

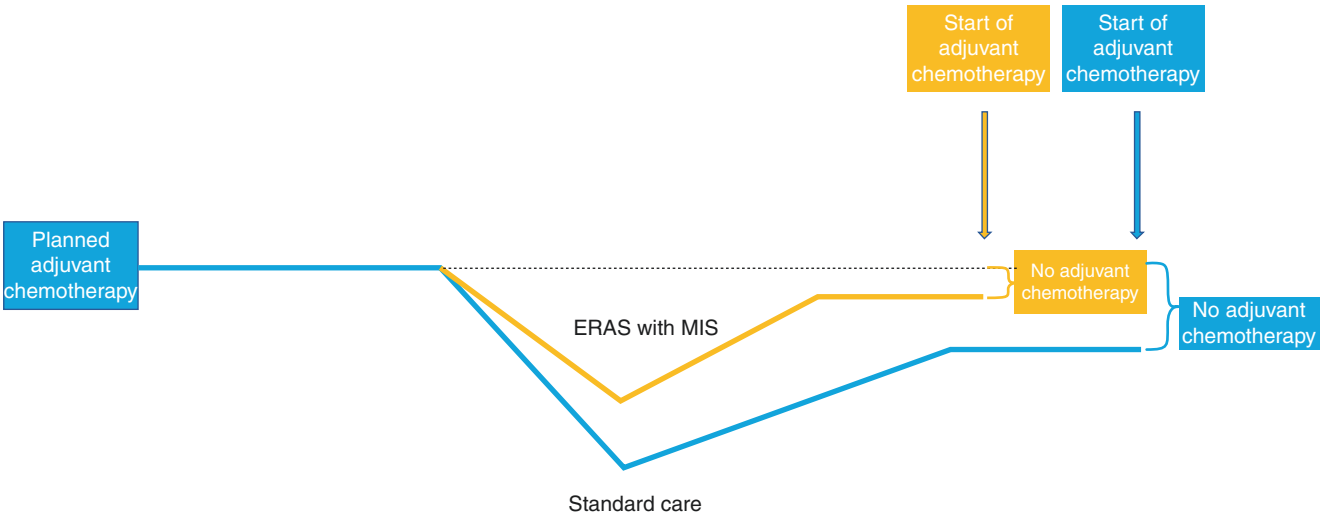

Fig. 26.2 Return to intended oncological therapy (RIOT). The perioperative effects of surgery on time to adjuvant oncological treatment in patients undergoing standard care and in an enhanced recovery setting. MIS minimally invasive surgery

87%) and increased cancer recurrence (19% vs. 15%) [12]. There was an obvious dose-response relationship showing gradually poorer oncological outcomes as the severity of complications increased. In a meta-analysis of randomized trials involving ERAS protocols, it was shown that implementation of ERAS resulted in a reduction in major hospital-associated infections (lung infections, urinary tract infections, and surgical site infections). The risk ratio was thus 0.38 (95% confidence interval [CI] 0.23–0.61) for lung infection, 0.42 (95% CI 0.23–0.76) for urinary tract infection, and 0.75 (95% CI 0.58–0.98) for surgical site infections [16].

Individual Component of ERAS and Long-Term Oncological Outcomes

Minimally Invasive Surgery and Long-Term Oncological Outcomes

Reducing the surgical trauma by minimally invasive surgery may result in long-term oncological improved outcomes based on the effect on the surgical stress response and on the reduced morbidity within 30 days after surgery. Several studies have shown that both within and outside an enhanced recovery program, minimally invasive surgery results in improved immune function: lower IL-6 and VEGF levels and higher insulin-like growth factor-binding protein 3 (IGFBP-3), natural killer (NK) cell, and HLA-DR concentrations. Meta-analyses including different oncological surgeries demonstrate that minimally invasive surgery reduces complications, intraoperative bleeding, and infectious complications [40–42]. In an RCT including 219 patients, it was shown that patients undergoing laparoscopic colectomy with Union for International Cancer Control (UICC) stage III disease had improved long-term survival. Recently it was also shown in patients with esophageal cancer that a hybrid procedure with open thoracic and minimally invasive abdominal procedure resulted in improved both short-term and long-term outcomes compared with the corresponding totally open procedure [43]. The disease-free survival did not reach, though, statistical significance. In a registry-based study, including only patients with UICC stage III colon cancer, it was also shown that the number of patients initiating chemotherapy within 4 weeks after laparoscopic surgery was statistically significantly higher in minimally invasive compared to open surgery [44]. In addition to the advantages due to preserved immune function, reduced inflammatory stress response, and reduced postoperative complications, minimally invasive hepatic surgery for hepatocellular carcinoma (HCC) may even reduce the number of circulating tumor cells [45]. There is an apparent imbalance between the strong experimental data and the few RCTs showing long-term oncological benefits and the meta-analyses demonstrating no advantage of minimally invasive surgery on long-term oncological outcomes [46, 47]. This apparent inconsistency may be due to the selection of patients where the advantage of reduced stress response is lower than the population that is usually not included in randomized clinical trials. Subgroup analyses investigating frailty, tumor stage, and maybe even immune phenotype or microbiome may clarify in the future whether certain subgroups of patients may have an even higher expected advantage of minimally invasive surgery. Future investigation including characterization of the immune phenotype of the patient combined with the tumor phenotype may in addition result in the identification of patient groups that should be offered oncological "inferior

surgery" due to a high risk of postoperative complications. It could be hypothesized that a patient with an apparently small tumor in the colon (clinically UICC stage I colon cancer) with a poor immune phenotype or high degree of frailty and/or comorbidities may benefit from a combined endoscopic-laparoscopic procedure with excision of the tumor without segmental hemicolectomy. Advantages have been demonstrated for patients with adenomas, showing that combined endoscopic-laparoscopic procedure results in improved recovery and reduced complications compared with the corresponding laparoscopic procedure with segmental resection [48]. Future studies should investigate whether this can be demonstrated in oncological patients.

Analgesia in ERAS Protocols and Long-Term Oncological Outcomes

The potential benefits of multimodal analgesia may be through its opioid-reducing effect and effects on early mobilization, reduced ileus, or early oral nutrition [49]. In addition, the individual components of a multimodal analgesic regime including epidural blockade or use of nonsteroidal anti-inflammatory drugs (NSAIDs) may have a separate effect on the metastatic process. As described elsewhere in this book, there is substantial evidence supporting the opioid-sparing effects of a multimodal analgesic regime. The use of morphine has in several studies shown to induce growth promotion and cell migration in tumor cells [50]. Morphine may also have a direct effect on the endothelial cells by preparing the prometastatic niche. In experimental models, several studies have shown that morphine can promote both lung cancer and breast cancer metastases [51, 52]. Preliminary research has also shown these associations in clinical studies. This has been demonstrated in patients undergoing analgesic treatment for prostate cancer and lung cancer. A central mechanism leading to cancer progression may be the mu opioid receptor. The mu opioid receptor is found in many non-neuronal tissues including immune cells and tumor cells. Thus, a high expression of mu opioid receptor has been found in colon cancer and prostate cancer tissues. In addition to these effects, morphine may also reduce tumor cell apoptosis, promote angiogenesis through VEGF, and suppress NK cell activity. A high use of opioids in the perioperative period may add to the prometastatic phenotype through direct effects on micrometastatic areas, circulating tumor cells, and suppressive effects on the cytotoxic immune response. Use of opioid-sparing anesthetic/analgesic techniques may result in improved clinical outcomes. This has been shown in pioneering studies by Buggy and colleagues who, in a retrospective study, reported that the use of paravertebral anesthesia significantly improved recurrence-free and metastatic-free survival compared with general anesthesia with opioids [53]. In patients undergoing surgery for esophageal squamous cell carcinoma, the authors investigated the association between opioid use within a 10-day period after surgery and long-term oncological outcomes. In a propensity-matched analysis of 285 patients, it has been shown that high-dose postoperative opioid use was associated with a significantly higher hazard ratio for recurrence (hazard ratio 2.16; CI 1.58–2.95) [54].

Use of epidural blockade may also per se confer an advantage due to the reduction of the endocrine metabolic stress response. In 588 patients undergoing colorectal cancer surgery, it was shown in a Dutch study that the 5-year survival rate was 51% in the group treated with epidural analgesia compared with 42% in the no-epidural analgesia group. The advantage was present after adjusting for confounders and was even higher for the elderly patients [55].

The same results were also found in another study of 749 patients undergoing colorectal cancer surgery where the 5-year survival rate was 62% in the epidural analgesia group compared with 54% in the group without an epidural. Again, in a subgroup of patients with higher American Society of Anesthesiologists (ASA) class, the 5-year survival was even greater [56]. Finally, a survival advantage was also demonstrated in a randomized trial including 177 patients undergoing colon cancer surgery with epidural analgesia, but this result was only seen in the first 1.46 years after surgery [57].

An integrated part of regional blockade is the use of amide anesthetics. The effect of amide anesthetics on blocking nerve impulse propagation is ideal for treating perioperative pain in patients with cancer. The positive effects may be through a direct cytotoxic effect of local anesthetics on tumor cells including the inhibition of cellular pathways that are crucial for tumor progression. Amide anesthetics may in addition have a direct cytotoxic immune stimulatory effect. Thus, studies have shown that amide anesthetics may promote NK cell cytolytic activity. In addition, amide anesthetics may block the negative effects of the pro-inflammatory stress response by attenuating TNFα (alpha)-induced effects. Finally, the effects of amide anesthetics may be on subcellular levels by affecting Akt pathway and production of MMP-9 [58]. These aforementioned potential benefits are based on experimental studies. Several retrospective studies have shown long-term oncological benefits by the use of amide anesthetics in patients undergoing surgery for malignant melanoma or breast cancer. Larger prospective trials are warranted before definitive conclusions can be made.

NSAIDs are an integral part of a multimodal analgesic regimen in many surgical procedures. Depending on the COX selectivity, the side effect profile varies considerably. In cancer surgery, use of the COX 2 selective NSAIDs, such as diclofenac and celecoxib, has proven to increase the risk of anastomotic dehiscence [59]. The same effects have not been shown in other NSAIDs such as ibuprofen. At the same

time, several studies suggest a pronounced anti-inflammatory response with the use of NSAIDs and even indicate a lower recurrence rate after surgery for breast cancer and hepatocellular carcinoma [60, 61]. The mechanism by which NSAIDs reduce recurrence rate is believed to be through inhibition of the tumor-associated inflammation and reduction of angiogenesis and lymph angiogenesis. This is primarily by targeting the COX-2 inflammatory pathway, which relies on prostaglandins. Prostaglandins have been shown to be essential for the tumor metastatic process. In addition to the prostaglandin inhibition and COX-2 pathway, NSAIDs also increase the expression of HLA class I and HLA-DR antigens of cancer cells. In an unpublished study, the use of NSAIDs in the immediate postoperative days in patients undergoing colorectal cancer surgery has been associated with reduced recurrence rate even after controlling for a higher risk of postoperative anastomotic leakage. Future multimodal prospective RCTs could thus include NSAIDs due to their immune modulatory and anti-inflammatory effects and direct effects on the tumor microenvironment.

Antimicrobial Prophylaxis and Mechanical Bowel Preparation

Bacteria in the bowel maintain the epithelial mucosal barrier function. In addition to this, colonic bacteria also break down ingested nutrients that can be more easily absorbed. The interaction between the bacteria in the bowel and the immune system leads to a maturation and development of both the adaptive and innate immune systems. The commensal bacteria also result in a local milieu where colonization from pathogenic bacteria is prevented. The surgical stress response results in a dramatic change in the gut microbiota with both changes in the density of bacteria and function of these. This does not only happen in abdominal surgery where bowel resection is involved but can also be seen in patients having a burn injury. Obviously, a resection of the bowel will also result in a significant change in the mucosa-associated bacteria with several hundredfold changes in the abundance of specific bacteria such as *Shigella* and *Enterococcus* species.

In recent years, there has been a major focus on the effects of mechanical bowel preparation and oral antibiotic treatment on the risk of postoperative surgical site infections and, secondarily, the risk of cancer recurrence [62]. Pathogens in the bowel such as *Enterococcus faecalis* may, through high collagenase activity and through activation of MMP9, be leading to tissue breakdown and intestinal inflammation. Secondarily, the *E. faecalis* may also have an effect on the macrophages related to tissue healing, which might induce epithelial to mesenchymal transition in tumor cells and thereby a prometastatic phenotype.

Recent major registry-based studies indicate that a combination of mechanical bowel preparation and oral antibiotics may reduce the anastomotic leak rate [63]. It has been shown that combination treatment with mechanical bowel preparation and antibiotics reduces significantly the content of enterobacterial species. This may be associated with reduced systemic inflammation and secondarily reduced risk of recurrence. As mechanical bowel preparation also leads to a higher risk of perioperative dehydration in specific patient groups, it should be investigated further in the future which patients should be offered mechanical bowel preparation and oral antibiotics before cancer surgery.

Perioperative Fluid Management

Fluid management is a central component of ERAS. Goal-directed fluid therapy (GDFT) is aimed towards giving the right amount of fluid at the right time in the perioperative setting. Both too liberal and too restrictive fluid therapy strategies may have negative consequences. The right amount of fluid therapy including type and timing has to be based on a dynamic understanding of the hemodynamics in the perioperative period. By the use of minimally invasive techniques, cardiac output can be measured in the perioperative period leading to an optimized fluid therapy. Both arterial line-based pulse contour analysis and Doppler flow-based technologies may be used. The aim is to obtain the ideal perfusion at all times and thereby oxygen delivery.

The beneficial effects on long-term oncological outcomes have been demonstrated in the study by Gustafsson et al. where patients receiving less than 3000 milliliters of fluids on the day of surgery had reduced cancer-specific death rates compared with the group receiving more than 3000 milliliters [64]. The significant difference was maintained after multivariate adjustments.

It is hypothesized that in oncological surgery, beneficial long-term effects of goal-directed fluid therapy may be related to reduced postoperative complications and, in particular, reduced infectious complications. However, in the context of overall management using ERAS protocols, GDFT may not have as much a benefit as in traditional care pathways [65]. By preventing systemic inflammation and suppression of the adaptive immune system, an optimized fluid therapy may translate into improved long-term oncological outcomes. Finally, GDFT may also remove the necessity to give patients postoperative transfusions, leading again to a theoretical benefit on the long-term oncological outcomes. However, recent major randomized clinical trials have not demonstrated the same effects. Subgroup analyses including only oncological patients should be performed in order to identify certain

patients in specific high risk of recurrence who may benefit from an intervention with GDFT.

Early Oral Intake

Nutrition in patients scheduled for major surgery is a substantial challenge. In various reports, it has been shown that one out of three patients scheduled for oncological surgery is malnourished. The background for this malnutrition and weight loss is due to the catabolic effects of the tumor, tumor-induced anorexia, mechanical obstruction of the GI tract by the tumor, and reduced oral intake due to pain and anxiety. There is no gold standard for nutritional assessment even if there exist more than 30 nutritional risk assessment tools. However, it is important to have a thorough assessment of the patient's nutritional status. The surgical stress response leading to pain, postoperative nausea and vomiting, immobilization, and bowel dysmotility and placement of nasogastric tubes due to traditional practice may all compromise oral nutrition after surgery leading to an even higher risk of postoperative complications, which may subsequently translate into poor oncological outcomes.

Randomized clinical trials including patients with ovarian cancer and major gastrointestinal surgery indicate that early oral feeding may translate into a reduced risk of postoperative complications and improved immune response. In 143 patients undergoing surgery for ovarian cancer, early oral postoperative feeding was associated with reduced postoperative complications and infectious complications compared with traditional oral feeding [66]. No differences were found in other short-term outcomes such as analgesic treatment, nausea, and vomiting. In an RCT of patients undergoing major gastric intestinal surgery, indicators of immune response (measurement of subpopulations of lymphocytes) were measured in patients receiving a nasogastric tube with early enteral nutrition compared with water. The authors showed a preserved adaptive immune response with a higher number of NK cells and larger expression of HLA-DR in the early feeding group [67]. Both these results indicate that early nutrition may, through reduced complications and improved immune response, result in improved long-term oncological outcomes.

Overall Effect of ERAS on Patient-Reported Outcomes

The complexity of surgery differs across surgical domains, disease, and most importantly the phenotype of surgical patients. Little knowledge has been reported on proper validated patient recovery measures and quality of life in patients undergoing surgery in ERAS settings [68, 69]. Identification of useful core, generic recovery parameters has so far been unsuccessful, and none have reached consensus in the broader surgical community, reflecting the issues of transferability and comparability across surgical disciplines [70].

In 2018, the Standardized Endpoints in Perioperative Medicine Initiative published a systematic review and consensus statement on patient comfort outcomes in clinical trials within the ERAS setting [71]. Outcome measures included pain intensity (at rest and during movement) at 24 hours postoperatively, nausea and vomiting (0–6 hours, 6–24 hours, and overall), one of two measures of quality-of-recovery (QoR score or QoR-15), time to gastrointestinal recovery, time to mobilization, and sleep quality. These endpoints should be incorporated in the design of surgical clinical trials in order to support future benchmarking and provide the groundwork for data pooling, meta-analyses, and exploration of long-term impact. Although very important for future work and understanding of perioperative pathophysiological dynamics, none of the proposed endpoints directly cover long-term outcome measures beyond 30 days after surgery. ERAS is indeed a well-established generic approach proven instrumental for optimal surgical recovery, but patient-centered recovery outcomes may not be considered generic or transferrable across surgical procedures. Furthermore, the value of the proposed outcomes may change over time according to the different stages of the recovery process and disease in question. In this perspective, little is actually known about what matters most to patients long term. Interestingly and very importantly in this context, discrepancy between objective measures and patient-reported outcomes (PROs) has shown to differ substantially [72].

Few properly designed studies have investigated the recovery of patients in the ERAS setting. Furthermore, studies do often not include validated techniques. The information on long-term post discharge recovery is of increasing importance as convalescence from surgery has shifted to the outpatient setting, as time in hospital has decreased dramatically in the past decades. As an example, the pioneering work by Henrik Kehlet revealed that acute postoperative pain was accompanied by persistent pain in 10–50% of patients following common types of surgery [73]. Specifically for colorectal cancer patients, the incidence of chronic pain has been described as high as 17% of patients undergoing major colorectal cancer surgery [74].

A recent study by Deiss et al. investigated PROs at 6 months after colorectal cancer surgery in an ERAS setting [75]. A total of 324 consecutive patients were included in the study. In total, 19% of patients reported persistent surgical pain, 20% of patients reported readmission, and 14% of patients reported less than complete satisfaction with their hospital stay. Of the patients reporting pain, 63% of patients reported taking medi-

cation, more than half of whom were taking opioids. The authors did not identify any association between preoperative pain levels and 6-month outcomes, nor were preoperative pain levels associated with higher postoperative pain levels. Of the patients reporting less than complete satisfaction with their hospital stay, postoperative pain and the occurrence of postoperative complications were the most prominent reasons. Shida et al. evaluated the QoR-40 questionnaire in a Japanese cohort of patients undergoing primary colorectal cancer resection using an extensive local ERAS protocol [76]. The QoR-40 is a 5-point Likert scale patient-rated questionnaire designed to measure across five dimensions of patient recovery. The authors investigated quality of recovery (QoR) at POD 1, 3, 6, and 30 days after surgery compared with a baseline preoperative status. A total of 90 consecutive patients were enrolled in the study with a mean age of 67.7 years. As for other studies within the ERAS literature, laparoscopic surgery was only applied in under half of the cases, and the study presented a median length of stay of 7.8 days. Across all five dimensions, patients' QoR scores decreased at POD 1 but recovered at POD 30, including dimensions of physical comfort and pain. The authors identified patients of young age and rectal tumor location as risk factors of poor recovery. The surgical approach being either laparoscopic or open did not influence early recovery after ERAS surgery.

Jakobsen et al. investigated the effect of ERAS implementation on convalescence after colonic surgery compared with conventional care in a Danish cohort of patients [77]. The main outcomes included fatigue, need for sleep, instrumental activities of daily living (IADL), basic activities of daily living (BADL), need for social and home care, contact with general practitioners, and readmission rate. The study was performed in a prospective, controlled, non-randomized interview-based design comparing outcomes in 194 patients undergoing open colonic surgery. Patients undergoing colonic resection in the fast-track program regained functional capabilities earlier, with less fatigue and need for sleep compared with conventional care. The patients subjected to fast-track surgery were discharged earlier than using conventional postoperative care, but the authors found no difference in need for home care, social care, or general practitioner (GP) visits. In spite of higher readmission rates (20% vs. 10%) in the fast-track group, the total mean hospital stay was shorter in the ERAS group (4.2 days vs. 8.3 days).

Organ-Specific Interventions in an ERAS Setting

Postoperative recovery after ERAS surgery constitutes a complex set of outcomes, which needs further investigation and consensus clarification—preferably in the context of specific diseases and surgical procedures using modern updated techniques. Organ-specific interventions deserve mentioning and may confer excellent strategies toward improvement of outcome after surgical procedures as there is currently a clinical need for stratified perioperative interventions according to patient phenotype.

Postoperative Pulmonary Complications

Postoperative pulmonary complications (PPCs) are frequent complications encountered after major abdominal surgery. The reported incidence of PPC is more than 10% after non-cardiac surgery [78]. Among other factors, prior medical history of chronic obstructive pulmonary disease (COPD), smoking history, duration of surgery, age, and high ASA class status are risk factors for PPC.

In 2018, Boden et al. published the results of a pragmatic multicenter randomized placebo controlled trial investigating the effect of preoperative physiotherapeutic interventions prior to surgery [79]. The authors compared preoperative physiotherapeutic education and training against standard care. A total of 441 patients were randomized to preoperative 30 minutes face-to-face physiotherapy education and training sessions within 4 weeks of surgery. The primary outcome included PPCs within 14 postoperative days or hospital discharge. From postoperative day 7 and onward, the assessors evaluated PCC only in clinical suspected cases. Overall, 20% of all patients experienced PPC. The intention to treat analysis showed an absolute risk reduction of 15% (95% CI; 7–22%, $p = 0.001$) when adjusted for differences in baseline variables. The number needed to treat was 7 (95% CI; 5–14). Secondary outcomes included postoperative infectious pulmonary complications. Hospital-acquired pneumonia was halved in the physiotherapy group compared with standard care. The number needed to treat was 9 (95% CI; 6–21). The authors found no difference in hospital length of stay, unplanned readmissions, or length of stay in intensive care units. PPC was associated with increased mortality at all time points after surgery. Subgroup analysis identified preoperative physiotherapy as a main driver of better postoperative short-term outcome after colorectal cancer surgery. A post hoc per protocol subgroup analysis indicated a 12-month survival benefit in participants educated by an experienced physiotherapist. The results of the study are in line with previous findings. A previous Swedish trial found a similar reduction in PCC of 78% after abdominal surgery [80].

Myocardial Injury After Non-cardiac Surgery (MINS)

Myocardial injury after non-cardiac surgery (MINS) is a significant clinical finding after CRC surgery [81]. MINS is

associated with mortality after surgery due to major vascular complications. Patients diagnosed with cardiovascular disease going into surgery have a higher risk of MINS. Recently the MANAGE (Management of Myocardial Injury After Noncardiac Surgery) trial, a multicenter international RCT, investigated the impact of twice daily 110 mg dabigatran compared with a placebo [82]. The primary endpoint was occurrence of major vascular complications (vascular mortality, nonfatal myocardial infarction, nonhemorrhagic stroke, peripheral arterial thrombosis, amputation, and symptomatic venous thromboembolism) up to 2 years after randomization (postoperative MINS after surgery). Safety outcomes included a composite of life-threatening, major critical organ bleeding. A hazard ratio (HR) of 0.72 (95% CI; 0.55–0.93, $p = 0.0115$) was found in the dabigatran group. The safety outcomes were not statistically significant, HR 0.92 (95% CI; 0.55–1.53, $p = 0.76$). Among patients with MINS, dabigatran 110 mg twice daily lowered the risk of major vascular complications, with no significant increase in major bleeding. An estimated 8 to 10 million people develop MINS each year, making this condition a potential major driver of postoperative adverse outcomes and a potential target for perioperative interventions [83]. Most ERAS protocols are developed on a one-size-fits-all backbone, which does not take individual needs into consideration. Stratified perioperative treatment alongside the fundamental principles of ERAS using, e.g., early mobilization, no excess use of drains, and early feeding should call for investigations. Adding dabigatran and preoperative physiotherapy counseling may improve patient outcomes dramatically. However, the important patient identification tools are missing, and current protocols do not consider organ-specific targeting.

Conclusion

A multitude of factors in the perioperative period has an impact on short- and long-term outcomes after oncological surgery. These factors are both unmodifiable patient-related risk factors and modifiable factors related to surgical approach and perioperative treatment protocols. There are apparently essential elements in the ERAS approach that may have instrumental effects on long-term oncological outcomes. Important aspects are the magnitude of adherence to ERAS, anesthetic modality, analgesic treatment, and magnitude of surgery. There is ample experimental evidence and limited clinical observational studies supporting this. The high-quality clinical evidence, however, is generally lacking. Within the next few years, the results from major multi-institutional and multinational randomized clinical trials examining anesthetic modality may help us better understand the importance of the intraoperative exposure of the oncological patient to different stressors, such as choice of intravenous or inhalational anesthesia. In general, there is a need for greater understanding of the individual risk factors for the patient scheduled for oncological therapy in order to tailor the right treatment protocol for the right patient at the right time by the right team.

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Postoperative Ileus: Prevention and Treatment

27

Alfred Adiamah and Dileep N. Lobo

Introduction

Postoperative ileus (POI) is the transient cessation of gut motility after surgery. The original Greek derivative of ileus, εἰλεός (*eileós*), describes "intestinal twisting" and is more synonymous with classical descriptions of volvulus and intussusception [1]. However, modern usage refers to the paralysis of gastrointestinal (GI) motility rather than a mechanical obstruction [2]. POI commonly occurs after gastrointestinal surgery but is also reported in other types of surgery (including orthopedic, gynecological, and urological surgery) [3–6]. It is associated with increased patient morbidity, length of hospital stay (LOS), and hospital costs [7–9]. Some studies have reported an increase in 30-day readmission rates [10] in patients who develop POI. A nationwide population study from the United States found that POI occurred after up to 19% of abdominal operations, leading to a prolonged mean LOS (11.5 days vs. 5.5 days) and costing substantially more ($18,877 vs. $9460) per patient who develops POI. The total estimated annual cost of POI to the US health economy was estimated as $1.46 billion [7]. Therefore, approaches to prevent and treat POI have been research priorities, especially in the era of enhanced recovery after surgery (ERAS).

Definitions

In classical literature, the *sine qua non* of ileus was defined by the clinical triad of abdominal pain, obstipation, and vomiting—symptoms present in most causes of bowel obstruction as well [1, 2]. Current definitions require a postoperative period, the absence of a mechanical obstruction, and an expanded scope of symptoms that includes abdominal distension, abdominal pain, nausea, vomiting, obstipation, and an intolerance to fluids [2].

Intra-abdominal surgery, and in particular surgery involving mobilization and resection of the bowel, is expectedly associated with a transient period of impaired gastrointestinal tract motility—a so-called physiological ileus [2, 11]. This period of transient physiological cessation of gut motility appears to be a part of the physiological response to the stress of surgery. The duration of this physiological ileus varies and reportedly lasts up to 24 hours in the small bowel, 24–48 hours in the stomach, and 48–72 hours in the colon [11, 12]. Duration of symptoms longer than 3–5 days would be atypical for physiological ileus. Therefore, persistence of symptoms at 3 days for laparoscopic surgery and 5 days for open surgery—in the absence of a mechanical cause, or overt postoperative complication such as an anastomotic dehiscence or intra-abdominal collection—meets the current definition of postoperative ileus (Tables 27.1 and 27.2) [2, 11].

Table 27.1 Definitions of postoperative ileus (POI) [2, 11]

POI	Transient cessation of coordinated bowel motility after surgical intervention, which prevents effective transit of intestinal contents or tolerance of oral intake
Primary POI	Occurs in the absence of any precipitating cause
Secondary POI	Ileus in the presence of a complication (e.g., sepsis, anastomotic leak)
Recurrent POI	Is the occurrence of ileus after an apparent resolution of the immediate POI
Prolonged POI	>3 days for laparoscopic surgery >5 days for open surgery

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Table 27.2 Sub-classification

Type	Definition
1	Affects the entire gastrointestinal tract with nausea, vomiting, and a failure to pass flatus or stool
2	Affects the upper gastrointestinal tract with nausea and vomiting, but with the presence of colonic activity
3	Manifests as no passage of flatus and/or stool, but with tolerance of diet

Reprinted with permission from Bragg et al. [11]

Pathophysiology

Gastrointestinal peristalsis allows propulsion of intestinal contents, while segmentation contractions ensure mixing of ingested materials [13]. These motor patterns are achieved through coordinated activity between the central and peripheral nervous system, with involvement of sensory and hormonal networks, smooth muscle cells, and gut flora [11]. This complex system of interaction is potentially disturbed by the physiological response to surgical stress in primary postoperative ileus or to the secondary insults such as collections or anastomotic leak as occurs in secondary POI [2, 12]. The overall consequence of a disturbance to any of the neuronal, sensory, motor, and hormonal pathways is disorganized electrical activity and paralysis of the affected intestinal segments [11]. This lack of coordinated electrical activity disables the propulsive action of the gut with the resultant intraluminal accumulation of gas and fluid—the clinical consequences of which are abdominal distention, pain and discomfort, nausea and vomiting, and an intolerance to oral intake [11].

Neural reflexes activated during and immediately after surgery mediate the first phase of POI. Sympathetic activity and an increase in adrenergic motor neuronal activity following the skin incision lead to the release of corticotrophin-releasing factor, which has an inhibitory effect on gut motility and precipitates the initial acute intestinal paralysis [14]. Noradrenergic pathways are also implicated in the initial arrest of peristalsis [15]. However, the use of beta-blockers to modulate gut response to adrenergic stimulation has not been shown convincingly to be beneficial [16].

The inflammatory response to surgery mediates the second phase of POI, which is thought to occur 3–4 hours after surgical manipulation. The release of cytokines and chemokines, which are proinflammatory mediators, causes the activation of phagocytes and migration of leukocytes to the *muscularis externa* [17, 18]. Activated phagocytes in turn release hormonal mediators such as nitrous oxide and prostaglandins, which directly inhibit smooth muscle contractility. Acetylcholine can reduce cytokine release by intestinal macrophages [19], and it has been proposed as a mechanism of modulating or attenuating the inflammatory response to surgery during the second phase of POI. Other pathophysiological mechanisms include direct bowel handling. Over-manipulation of bowel appears to lengthen the duration of POI potentially by increasing the systemic inflammatory response. Bowel handling is minimized but not obviated in minimal access procedures, and in these instances the incidence and duration of POI are also consequently reduced [11].

Electrolyte disturbance is one of the commonly ascribed causes of all paralytic ileus and includes hypokalemia, hypocalcemia, and hypomagnesemia. Smooth muscle contractility is dependent on extracellular calcium influx through voltage-dependent calcium channels whose depolarization is intrinsically dependent on potassium. However, the state of potassium and its bioavailability are linked to magnesium. Therefore, electrolyte disturbances of any of these key electrolytes involved in effective smooth muscle contractility are implicated in all causes of paralytic ileus [20, 21].

The perioperative use of fluids, and in particular crystalloids, has shown them to be important mediators of delayed gastric motility and function. The mechanisms are not entirely clear, but fluid overload induces edema, which at the molecular level interferes with the activation of signal transduction and synthetic pathways involved in inducing smooth muscle contractility such as activator of transcription-3 and NF-kB [21]. Avoidance of salt and water overload is now advocated to prevent fluid overload and ensure judicious intraoperative fluid administration guided by stroke volume/cardiac output monitoring [20].

Given the complexity of the pathway that controls peristalsis, it is appreciable that the sympathetic inhibitory reflexes—stress responses, inhibitory mediators of the inflammatory response, humoral agents, and anesthetic and opioid analgesic agents—all to some extent play a role in its pathophysiology. This understanding of the complexity of its pathogenesis (Fig. 27.1) mandates a polymodal approach to its prevention and treatment.

Risk Factors

Risk factors and possible mechanisms for POI are summarized in Table 27.3 [22–30].

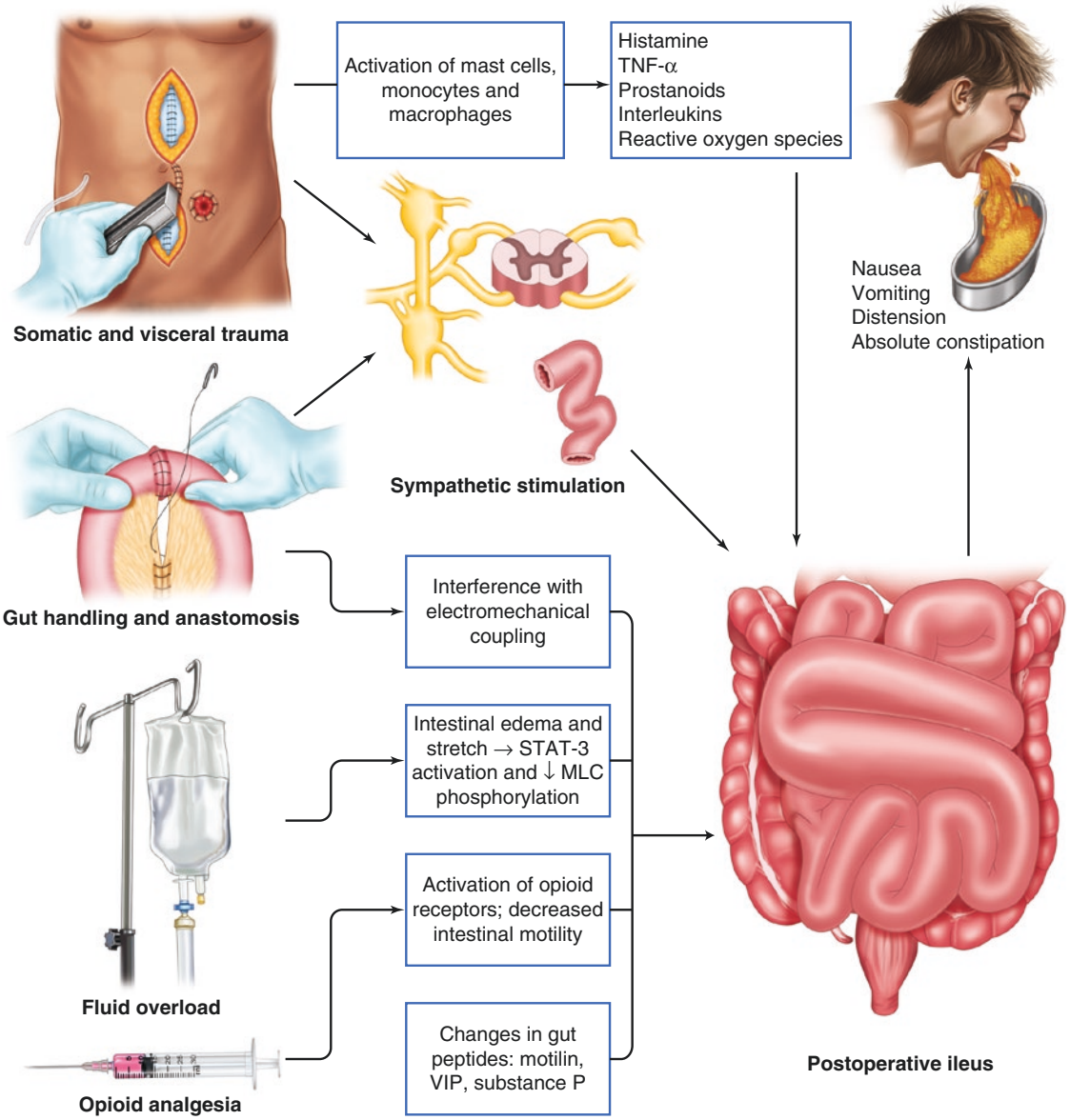

Fig. 27.1 Schematic diagram showing proposed mechanisms for the pathogenesis of postoperative ileus. (Adapted with permission from [11])

Table 27.3 Risk factors for postoperative ileus

Risk factor	Possible mechanisms
Increasing age [22, 23]	Reduced overall capacity for the body to recover from surgical insult [23]
Male gender [24]	Increased inflammatory response to surgery [25] Increased pain threshold in males [26], resulting in higher catecholamine release [27]
Low preoperative albumin [24]	Increased edema and stretch of gut
Acute and chronic opioid use [22, 28]	μ(mu)-opioid receptor stimulation ameliorates peristalsis [23, 29]
Previous abdominal surgery [22]	Increased need for adhesiolysis, increased bowel handling
Pre-existing airways/peripheral vascular disease [24]	Reduced physiological reserve
Long duration of surgery [24, 28]	Increased bowel handling [30] and opiate use
Emergency surgery [25, 26]	Increased inflammatory and catecholamine response; secondary causes of POI
Blood loss and need for transfusion [22–24, 28]	Increased crystalloid administration resulting in edema
Procedures requiring stomas [25]	Edema in abdominal wall muscle and cut bowel

Adapted from Ref. [11]

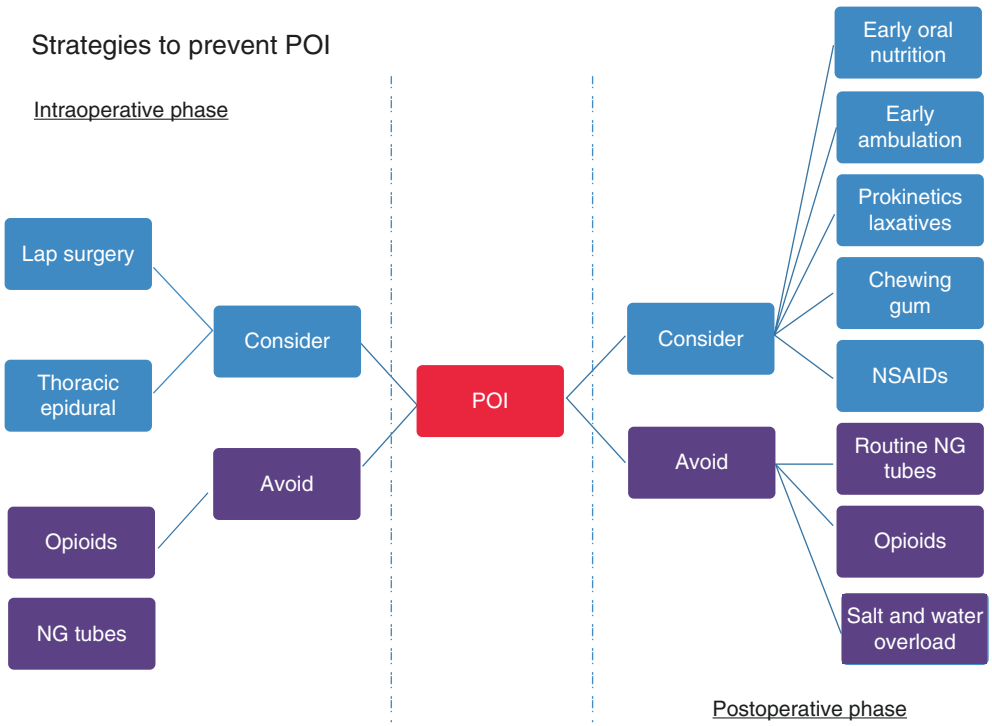

Fig. 27.2 Preoperative, intraoperative and postoperative approaches to reduce the risk of postoperative ileus (POI). Lap laparoscopic, NG nasogastric, NSAIDs nonsteroidal anti-inflammatory drugs

Complications of Ileus

The clinical consequences of postoperative ileus include aspiration of enteric contents and, therefore, aspiration pneumonia [2, 31]. Fluid and electrolyte imbalance and a disturbance in renal function also occur not too infrequently [20, 32]. Nutritional deficits, malnourishment, and its sequelae, such as impaired immunity and a risk of sepsis, further complicate the postoperative course in patients who develop POI [11]. Prolonged POI may necessitate the need for parenteral nutrition, which comes with associated risks. The cumulative effect of which is an increased length of hospitalization and increased treatment cost [7, 8].

The most important complication of postoperative ileus is the significant impact it has on the patient reported quality of life [33]. Every symptom of POI—distension, pain, and persistent nausea and vomiting—is all noted to negatively affect quality of life and impair clinical progress.

Management of Postoperative Ileus

The management approaches for POI can be subdivided into preventative strategies, supportive measures, and directed therapies. Perioperative approaches to prevent the occurrence of POI require a change in perception of its inevitability to recognition of this complication as a potentially avoidable event. Some of the strategies in prevention include choice of anesthesia, surgical technique, and postoperative analgesics (Fig. 27.2).

Supportive measures include early removal of nasogastric (NG) tubes or avoidance of routine NG intubation, early ambulation, early oral feeding, and prokinetic agents. These strategies have been incorporated into fast-track protocols designed to shorten POI and hasten discharge. The final component involves therapeutic interventions to reduce the duration of POI when it does occur. For some of these components, evidence is strong for their use, and for others evidence is weak or conflicting.

Prevention Strategies

Perioperative Phase

Salt and Water Management

The goal of perioperative fluid therapy is to maintain normovolemia and end-organ perfusion during surgery. However, surgery itself causes an increase in hormonal signaling pathways (via ADH, cortisol, and aldosterone) leading to both salt and water retention [32]. Excessive perioperative fluid administration can therefore compound the state of fluid retention and lead to an increase of 2–3 kg of body weight, as

a result of a redistribution of fluid to the interstitial spaces. While this can induce cardiopulmonary overload, the edema can also potentiate the risk of both POI and anastomotic leak [32, 34]. In a randomized controlled trial (RCT) by Lobo et al., patients who received liberal fluid therapy, when compared to a group receiving a more restricted fluid therapy intraoperatively, had almost double the gastric emptying time as well as increased time to passing flatus and to passing stool. They also had more complications and longer duration of in-hospital stay [20].

The administration of 0.9% saline alone in this setting further exacerbates the imbalance of both micronutrients and electrolytes, particularly Na^+, K^+, and Cl^-, which are central in facilitating smooth muscle contractility. Both under- and over-administration of fluid lead to complications. Techniques to support goal-directed fluid administration, such as esophageal Doppler, LiDCO (LiDCO Ltd., Cambridge, UK), or PiCCO (Philips Healthcare, the Netherlands), can be utilized to achieve this [32]; however, the evidence for benefit remains conflicting [35, 36]. The use of balanced fluids, to achieve a state with a negligible gain in weight, is the ideal.

Opioid-Sparing Analgesia

The routine use of opioids in the postoperative period, while an effective means of providing pain relief, is implicated in perpetuating POI. The negative effects of opioids can be avoided or substantially minimized by employing alternative analgesic options such as epidural analgesia and intravenous lidocaine.

Midthoracic Epidural Analgesia

Adequate postoperative analgesia is achievable with epidural analgesia (EA), eradicating the need for opioids. Additionally, there is accumulating evidence to suggest that EA with local anesthetic directly reduces the duration of POI due to its inhibitory effect on sympathetic nervous afferents to the gastrointestinal tract [15]. Several meta-analyses, and a Cochrane review comparing epidural analgesia with local anesthetic vs. systemic opioids in open abdominal surgery, demonstrated a reduction in gastrointestinal paralysis [37, 38]. However, examining the role of EA in laparoscopic surgery with regard to POI remains inconclusive [39, 40].

Intravenous Lidocaine

A randomized clinical trial comparing thoracic EA (TEA) with intravenous lidocaine demonstrated similar postoperative pain scores, duration of ileus, and LOS after colorectal surgery, [41] suggesting that the two approaches are equally efficacious. Typically, lidocaine is administered as an intravenous (IV) bolus (1.5–2 mg/kg) followed by a continuous infusion at 1.5–3 mg/kg/h for up to 24 hours postoperatively. The improvement in postoperative pain scores at 6 hours and 24 hours with the use of intravenous lidocaine and culminates in a reduction in total opioid consumption. This was confirmed in a meta-analysis that examined IV lidocaine vs. controls and demonstrated reduction in opioid use, shorter time to passage of flatus and to first bowel movement [42].

Surgical Approach

Minimally invasive techniques have been consistently shown to be associated with decreased postoperative pain, faster recovery time, and shorter length of stay for the majority of GI surgical procedures when compared with similar procedures undertaken as traditional open laparotomy. The decreased pain would coincidentally further reduce the need for opioid analgesia. A study that evaluated gastrointestinal transit time in both laparoscopic and conventional open surgery using radiopaque markers demonstrated faster transit in laparoscopic surgery patients [43]. These patients also had shorter time to first flatus and first bowel movement. The mean time to first passage of flatus and motion was 50 hours and 70 hours in laparoscopic cases and 79 hours and 91 hours in conventional cases ($P < 0.01$), respectively [43].

Nasogastric Tubes

Historically, the use of NG tubes in GI surgery, and in particular surgery requiring bowel anastomosis, was to decompress the stomach and reduce the risk of anastomotic leakage. However, this practice was without concrete evidence of benefit. More recently, the prophylactic use of NG tubes was examined by a Cochrane review in elective surgery [44–46]. The authors found that it had no impact on recovery of bowel function or protecting bowel anastomoses. Additionally, they found no reduction in pulmonary complications, no reduction in length of stay, and no benefit in improving patient comfort [44–46]. Contrastingly, time to first flatus was earlier in those without an NG tube (0.51 days earlier; WMD, 95% CI 0.45–0.56; $P < 0{\cdot}00001$). The current evidence therefore does not support the routine placement of NG tubes after GI surgery.

Postoperative Phase

Early Oral Feeding

The implementation of ERAS protocols, which include instigating early oral nutrition, has led to beneficial effect on reducing LOS [47] and infectious complications [48]. A recent meta-analysis of early oral nutrition [49] advocates its use for reduction in POI, having considered time to flatus, vomiting, and need for NG tube reinsertion. In these analyses there was no evidence of an increased risk of anastomotic leakage [47, 50] in patients who had early oral nutrition. A Cochrane review on early oral nutrition and postoperative complications [51] found no benefit in delaying feeding.

Prokinetics

As part of the multimodal approach to POI, prokinetics have been shown to play a role, with combination of 5-HT3 receptor antagonists with dexamethasone having been reported to be particularly effective [52]. Mosapride, a selective 5-HT4 agonist that acts as a gastroprokinetic, was investigated in two clinical trials that included patients undergoing colonic resection. In both studies there was a reduction of time to first flatus, first bowel movement occurring, and length of hospital stay (6.7 vs. 8.4 days). It has been suggested that the effect of mosapride on reducing POI may also be influenced by its anti-inflammatory properties on the GI tract [53].

Laxatives

The use of laxatives in colorectal surgery is recommended as part of a multimodal postoperative rehabilitation program [54]. Investigations of its use to prevent or ameliorate POI largely come from studies on gynecological surgery [55, 56]. An RCT in women undergoing abdominal hysterectomy [57] demonstrated a reduction in median time to first postoperative defecation from 69 hours in the placebo group to 45 hours in the laxatives treated group ($P < 0.0001$). The combination of postoperative laxatives and oral nutritional supplements on gastrointestinal function was further investigated in a study of patients undergoing liver resection in an enhanced recovery setting. Those receiving laxatives passed stool at 4 days (3–5 days) and those not receiving laxatives at 5 days (4–6 days); $P = 0.034$. Oral nutritional supplementation in this setting did not affect gastrointestinal recovery [58].

Chewing Gum

Chewing gum is a form of sham feeding that is thought to stimulate gastrointestinal recovery postoperatively without challenging the system with actual food. Studies on this topic have overwhelmingly been of poor methodological quality and have yielded conflicting results. A meta-analysis of 17 studies examining chewing gum after abdominal surgery demonstrated favorable results for gum chewing in time to first flatus, time to first bowel movement, and LOS [59]. Given the low side effect profile and emerging evidence, gum chewing could play a helpful role in a multimodal approach to POI. However, in a recent RCT where patients were managed with ERAS principles, chewing gum did not add a benefit [60].

Nonsteroidal Anti-inflammatory Drugs

The use of nonsteroidal anti-inflammatory drugs (NSAIDs) is advocated as part of a multimodal postoperative analgesic strategy that helps curtail opioid consumption. Interestingly, the mechanism of action of NSAIDs in inhibiting cyclooxygenase (COX) pathways is potentially exploited in reducing the incidence of POI. There is evidence from both animal [61] and human studies [62] to suggest that COX-2 inhibition shortens POI. This hypothesis was further examined in a trial of NSAIDs in abdominal surgery, which demonstrated a reduction in POI rates in the NSAIDs arm. Surprisingly, there was no difference in opioid usage between the NSAIDs arm and controls [63].

NSAIDs can impair the process of tissue healing and could, therefore, provoke failure of anastomosis healing. However, the results of the currently available studies on its negative side effects remain conflicting [63–68].

Alvimopan

Opioid analgesics exacerbate ileus through peripheral μ(mu)-opioid receptor action [11]. Alvimopan, a competitive μ(mu)-opioid receptor antagonist, has been proposed to alleviate postoperative ileus [69]. In studies of its use in open GI procedures, its use led to a shorter time of resolution of GI function and shorter length of hospital stay [69]. However, as opioid-induced impairment of gastrointestinal motility is only one of several pathophysiological mechanisms that precipitates ileus, it is very conceivable that its use will be limited [11]. Additionally, it is associated with significant cost outlay, with the most recent figures suggesting cost of $158 per 12 mg capsule. Alvimopan was seen to be beneficial in three phase III trials on surgery requiring bowel resections [70]. However, it had minimal benefit on gastrointestinal recovery in patients undergoing hysterectomies [71]. There was no significant benefit seen in patients undergoing laparoscopic surgery [72, 73] suggesting it is less useful in those scenarios. Likewise in the setting of an enhanced recovery program the impact of Alvimopan was reduced [74, 75]. Alvimopan still remains a promising drug and has a potential role in the treatment paradigm of POI. However, it must be noted that benefit appears to be limited to gastrointestinal surgery with bowel resection but is less relevant in cases of POI from non-resectional surgery.

Treatment

The treatment of POI is mainly directed at supportive therapy and symptom control. To avoid the risk of aspiration, NG tube placement for gastric decompression is the mainstay of treatment together with fluid and electrolyte replacements. Plain abdominal radiograph, with or without water-soluble contrast media (WSCM) such as Gastrografin, may aid the diagnosis—or at least helps with the exclusion of mechanical causes of small bowel obstruction. Cross-sectional imaging may also aid in identifying secondary causes of ileus, such as anastomotic leak and intra-abdominal collections.

Increasingly water-soluble contrast media (WCSM) are being employed as a therapeutic modality in adhesive small bowel obstruction [76]. It has been shown that patients administered Gastrografin who had contrast in their colon

were more likely to have POI resolve, obviating the need for surgical intervention [77]. Additionally, in these cases, there was a decreased LOS of −1.87 days [77]. While, it has utility as a diagnostic modality that encourages earlier decision-making, its therapeutic role is still debated. In POI, the diagnostic attributes of WSCM can be appropriated as the lack of contrast in the colon may delineate ongoing ileus. However, any therapeutic role of WSCM in this setting has not been examined.

Other Future Therapies

Several meta-analyses have demonstrated a reduction in postoperative opioid usage following intraoperative administration of magnesium. The reduction in opioid use would reduce the risk of POI attributable to opioid use. A small RCT [78] demonstrated a reduction in POI in patients receiving intravenous magnesium. The abundant presence of nicotinic acetylcholine receptors in the colon renders them important therapeutic targets. In healthy volunteers, nicotine administration resulted in a reduction in total colonic transit time [79]. However, these potential treatments require further rigorous study before they can be considered feasible treatment options.

Conclusion

Postoperative ileus is in itself a physiological response of the gastrointestinal system to the stress of surgery. The prolonged phase is, however, pathological and precipitated by multifactorial processes. It is for this reason that single agents used in isolation do not show significance in trials. The approach required to reduce the incidence and duration when ileus occurs lies in the application of preventative and supportive measures addressing the different underlying causes of this debilitating postoperative complication. Less use of opioids, avoidance of salt and water overload, no NG tubes or early removal of NG tubes, early initiation of oral intake, early mobilization and chewing gum are all likely to play roles in the multimodal, fast-track approaches to postoperative ileus.

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Antibiotic Prophylaxis and Surgical Site Infection Prevention

28

Ho-Seong Han and Do Joong Park

Introduction

Surgical site infection (SSI) refers to infection arising in the tissue, organ, or space that has been exposed during surgery. SSIs are classified as incision site or organ space infections. Incision site infections can be either superficial (occurring in the skin or subcutaneous tissue) or deep infections [1]. SSI is associated with the degree of bacterial contamination during surgery, the duration of surgery, and underlying conditions [2]. There are many risk factors for SSIs, such as older age, diabetes mellitus, immunosuppression, obesity, malnutrition, organ failure, anemia, chronic inflammation, poor skin preparation, inappropriate antibiotic prophylaxis, blood transfusion, hypoxia, hypothermia, prolonged surgery, and long hospital stays [3–5].

Pathogenesis

The interaction between bacterial invasion and host defenses can have several consequences, i.e., local infections (such as cellulitis, lymphangitis, and severe soft tissue infection) or systemic infection, which means that local defense mechanisms have been inadequate, resulting in increased morbidity and mortality. The condition can be worsened by the presence of systemic infection in conjunction with a serious local infection, and chronic abscesses may occur after intermittent drainage or bacteremia.

Infection can be defined as a condition in which bacteria are identified in tissues or the bloodstream, resulting in an inflammatory reaction. Redness, pain, fever, and edema are often found in infected areas. In healthy people with normal defense mechanisms, most infections cause systemic symptoms (such as elevated body temperature, increased leukocyte count, tachycardia, and tachypnea), in addition to local symptoms. These symptoms constitute the systemic inflammatory response syndrome (SIRS). SIRS can be caused by a variety of diseases, including pancreatitis, trauma, tumors, and blood transfusions, in addition to infection. SIRS arising as a result of infection is defined as sepsis and is caused by a series of processes that result from the release of inflammatory mediators after exposure to bacteria [6]. Inflammatory mediators include endotoxins produced by Gram-negative bacteria, peptidoglycan and teichoic acid from Gram-positive bacteria, and the cell wall components of yeast and fungi. The patient develops sepsis when the clinical diagnostic criteria of SIRS are present and there is a source of local and systemic infection. Severe sepsis refers to cases of sepsis with newly developed organ failure. Patients with sepsis who require mechanical ventilation that do not produce adequate amounts of urine despite a sufficient supply of fluid or have hypotension that requires vasoconstrictor treatment are considered to be highly likely to develop severe sepsis. Septic shock is defined by acute circulatory insufficiency with hypotension that persists despite an adequate supply of fluid. It is the most serious form of infection and is associated with a high mortality rate [7].

Pathogens

Common causes of infection in surgical patients include bacteria, fungi, and viruses (Fig. 28.1), with bacteria accounting for the majority of surgical infections. Gram-positive bacteria are the most common causes of infection in surgical patients, including aerobic skin bacteria (e.g., *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pyo-*

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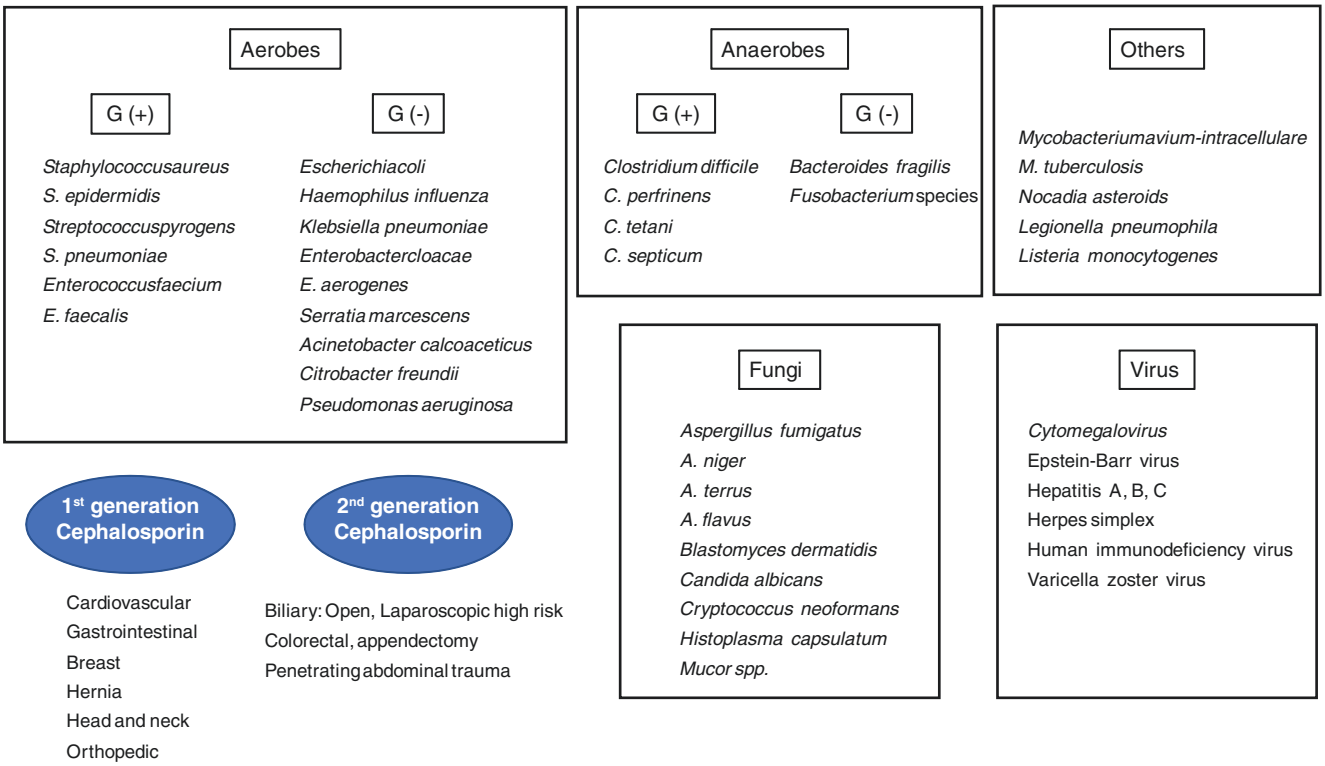

Fig. 28.1 Common pathogens of surgical site infection and prophylactic antibiotics

genes) and intestinal bacteria (e.g., *Enterococcus faecalis* and *Enterococcus faecium*). Aerobic skin flora account for a large proportion of surgical wound infections, either alone or in conjunction with other agents. Enterococci in patients with immunodeficiency or chronic illness cause nosocomial infections, such as urinary tract infections or sepsis. There are many Gram-negative bacterial pathogens that cause infection in surgical patients, most of which are *Enterobacter* species, such as *Escherichia coli*, *Klebsiella pneumoniae*, *Serratia marcescens*, *Enterobacter*, *Citrobacter*, and *Acinetobacter*. Other Gram-negative bacilli include *Pseudomonas* species and *Xanthomonas* species. Anaerobic bacteria do not produce catalase, a hydrogen peroxide-degrading enzyme that reacts with oxygen, and, therefore, cause infection in specific regions such as the oral cavity, colon, and rectum. The fungus *Candida albicans* causes nosocomial infections in surgical patients, and *Mucor*, *Rhizopus*, and *Absidia* cause rare, severe soft tissue infections. Fungi, such as *Aspergillus fumigatus*, *Aspergillus niger*, *Aspergillus terreus*, *Blastomyces dermatitidis*, *Coccidioides immitis*, and *Cryptococcus neoformans*, cause opportunistic infections in immunodeficient patients. As viruses are small and multiply within cells, they are difficult to culture, and a clinical diagnosis can be delayed. As with fungal infections, viral infections often occur in surgical patients receiving immunosuppressive therapy after organ transplantation. Common viruses include *Adenovirus*, *Cytomegalovirus*, *Epstein-Barr*, *Herpes simplex*, and *Varicella zoster*. Careful attention should be paid to human immunodeficiency virus (HIV) or hepatitis B and C infections, which can be transmitted to healthcare providers through blood or body fluids. Therefore, appropriate precautions should be taken, such as the use of protective equipment and cleaning of hands and skin surfaces that have been in contact with infected patients.

Basic Principles of Prevention

The prevention of SSI refers to methods adopted to reduce infectious pathogens in patients, as well as external factors relating to the surgeons and the surgical environment, including mechanical and chemical approaches, antibiotic use, or a combination of these methods. Bacteria on the skin and intestinal surfaces can invade the body as a result of trauma, burns, or surgery. All staff in the operating theater should wash their hands and arms well with an antimicrobial solution and use aseptic techniques during surgery; the skin should be cleaned thoroughly prior to incision. If necessary, hair removal is also recommended, using a clipper or depilatory agent rather than a razor as small scratches can promote the growth of skin microorganisms. While these techniques reduce the presence of infectious agents, it is not possible to

sterilize the skin or other surfaces completely. Therefore, entering the soft tissue, or the gastrointestinal tract through the skin, is related to a degree of microbial contamination, and procedures such as colon resection, prosthetic valve insertion, or transplantation can introduce several types of infection. Antibiotic therapy is, therefore, an indispensable component of surgical procedures.

Control of the Source of Infection

The first rule when treating surgical infections is to drain abscesses, remove infected tissues, necrotic debris, and any foreign material, and manage any underlying diseases. Purulent fluid should be removed by percutaneous drainage or surgical incision. If there is a progressive source of contamination (such as bowel perforation), or an aggressive and rapidly spreading infection (such as a necrotic soft tissue infection), appropriate surgical management is required to remove sources of contamination and infected tissues and to eliminate the primary cause of infection. Other treatments, such as antibiotic therapy, are indispensable, but they should be used in addition to effective surgical management. In rare cases, severe surgical infections may be treated with antibiotic therapy only, but if contamination persists, antibiotic treatment alone will not resolve the disease. Antibiotic therapy alone is also accompanied by a high level of morbidity, and sometimes mortality, due to erroneous diagnosis or delayed incisional drainage while awaiting the results of additional diagnostic tests.

Use of Appropriate Antibiotics

Prophylactic use of antibiotics refers to the administration of drugs prior to surgery in order to reduce the number of microorganisms entering the tissue or body cavity. The selection of an antibiotic agent is based on knowledge of the patient's medical history and the type of microorganism common to the surgical site. For example, patients who are scheduled to undergo colonic resection should be treated with antibiotics that have antimicrobial action against skin flora, Gram-negative aerobes, and anaerobic bacteria (Fig. 28.1) [8]. First-generation cephalosporin such as cefazolin is appropriate for cardiovascular, gastrointestinal, breast, hernia, head and neck, or orthopedic surgeries. A second-generation cephalosporin, such as cefoxitin, is proper for biliary (laparoscopic high risk or open), colorectal surgery, appendectomy, or penetrating abdominal trauma surgery. The use of prophylactic antibiotics is, by definition, limited to the preoperative and intraoperative period, and single-dose antibiotics should be considered [8, 9]. However, additional doses should be administered during complex procedures or if the surgical duration exceeds the antibiotic half-life. There is no evidence to support the use of antibiotics after surgery, and therefore they should not be administered due to the additional costs and the risk of antibiotic resistance. In addition, antibiotic prophylaxis for infectious endocarditis is recommended in patients with cardiac disease undergoing surgical procedures [10].

Empirical therapy refers to the administration of antibiotics when there is a high risk of surgical infection during the course of an existing disease, such as perforated appendicitis or colon perforation. If antibiotic therapy is used because the patient is considered to be at high risk of infection during surgery, it cannot be divided into prophylactic and empirical use. Empirical antibiotic treatment is also indicated for patients with potential infectious agents or for critically ill patients with severe sepsis or septic shock. Empirical therapy should be used for only 3–5 days [11]. Empirical therapy is often difficult to distinguish from definite infection management. For surgeons, the choice of antibiotic is dependent on the results of microbiological identification and whether it is a single or multiple microbial infection. Infection with a single strain is usually a postoperative infection, including urinary tract infection, pneumonia, and bacteremia. If these patients exhibit evidence of local infection (such as chest X-ray infiltration and Gram-positive staining of sputum and sepsis), empirical treatment must be initiated. Appropriate antibiotic treatment should be undertaken using a step-by-step reduction method; i.e., broad-spectrum antibiotics are initially administered and treatment is adjusted according to the patient's response and the results of bacterial identification. Piperacillin-tazobactam, carbapenems, fluoroquinolones, or tigecycline can be used for broad-spectrum coverage. Metronidazole is used for the treatment of anaerobic bacteria [12–14]. The choice of the initial agent is dependent on culture results, and it may be selected according to institutional or center-specific susceptibility results. Antibiotic selection is crucial, as failure to select an appropriate agent can lead to a significantly higher rate of patient mortality. It is, therefore, crucial to obtain culture and susceptibility results within 24–72 hours. The patient's clinical course should be monitored closely, and additional tests should be performed after initial treatment.

In patients with multiple microbial infections, the primary approach is to eliminate the source of infection, although antibiotic therapy also plays an important role. In these patients, the bacterial culture results are less important as not all bacterial types will be identified. Therefore, the antibiotic prescription should not be revised on the basis of culture information alone, and clinical observations are of most importance. For example, patients who have undergone appendectomy due to perforated appendicitis or patients who have undergone intestinal resection should receive antibiotics for aerobic and anaerobic bacteria for 3–5 days. Once

bowel function is restored, intravenous antibiotics can be replaced by oral medication, which will facilitate early patient discharge. According to recent research on antibiotic selection for the effective treatment of intraperitoneal infection, antibiotics for aerobic and anaerobic bacteria have shown very similar results, and treatment failures resulted from factors relating to the removal of infection rather than antibiotic selection.

Duration of Administration

The duration of antibiotic treatment should be determined at prescription. Prophylactic antibiotics should be administered once, prior to skin incision; empirical treatment should be administered for 3–5 days and discontinued earlier if no local or systemic infection is observed. Long-term empirical antibiotic use is associated with increased mortality in critically ill patients who show no bacterial growth in culture and, therefore, should be discontinued when the infection is not proven. According to antibiotic treatment guidelines for single bacterial infections, the duration of antibiotic use for the treatment of upper respiratory tract infections is 3–5 days, pneumonia 7–10 days, and bacteremia 7–14 days. Longer periods of antibiotic use are not beneficial and serve only to increase the risk of overlapping infection by resistant bacteria. Antibiotic therapy for osteomyelitis, endocarditis, and artificial implants should be continued for 6–12 weeks. The choice of antibiotic should take into account susceptibility to the most sensitive, the least toxic, and inexpensive antibiotics, with susceptibility being the most important consideration. Severe or recurrent infections may require the use of two or more antibiotics. After 1–2 weeks of intravenous administration, oral administration may be considered if clinical improvement is observed and if oral administration can maintain therapeutic drug levels.

Most studies on the duration of antibiotic treatment for the management of infections resulting from multiple strains focus on patients with peritonitis. For perforated gastrointestinal tract lesions without extensive contamination, 12–24 hours of antibiotic therapy can be satisfactory. In the case of perforation or necrotizing appendicitis, 3–5 days of therapy is required; if the perforation of the gastrointestinal tract causes moderate contamination, 5–7 days is recommended, and in cases of extensive peritoneal contamination or in immunocompromised patients, 7–14 days of antibiotic treatment is indicated. However, surgeons' efforts to control the focus of the infection are more important than the duration of antibiotic use. In the treatment of severe intraperitoneal infections, the complete eradication of infection can be considered to have been achieved if there is an absence of leukocytosis and band-shaped polymorphonuclear leukocytes in the peripheral blood smear and if the patient's body temperature is <38.5 °C; antibiotic therapy can then be discontinued. However, the presence of one or more of these factors does not necessarily mean that antibiotic treatment should be continued or altered. Rather, it is necessary to determine if there is any cause of infection other than the peritoneal cavity or remaining intraperitoneal infection.

Antibiotic abuse, which is prevalent in both inpatients and outpatients, has economic consequences as well as the challenge of side effects (such as drug toxicity or allergies), the development of new infections (such as *Clostridium difficile* colitis), and the emergence of multidrug-resistant strains. Prophylactic antibiotics should be used only during surgical procedures, and empirical therapy should not be initiated if the objective criteria are not met. The duration of antibiotic use is determined from the time of first administration, and antibiotics should be discontinued immediately if there is no evidence of infection in clinical or microbiological examination, to ensure that the duration of antibiotic use is as short as possible. Prolonged use of antibiotics shows no benefit in patients with drain or tube placement.

Allergy to Antibiotics

Prior to prescribing antibiotic therapy, the patient's allergic status should be established. In patients with severe allergic reactions to penicillin, it is appropriate to avoid beta-lactam drugs that may exhibit cross-reactivity; carbapenem has a high level of cross-reactivity, while cephalosporin cross-reactivity is low and it is rare with the monobactams. If the patient has a serious allergic reaction to an agent, such as anaphylaxis, all drugs of that type should be avoided. Where there is no other option, clindamycin can be used for patients with beta-lactam allergies.

Classification of Surgical Site Infections

SSIs are classified according to the degree of bacterial contamination at the time of surgery [15]:

- Class 1 denotes a clean wound that is not infected (e.g., breast and hernia surgery), where the wound may be infected by skin flora only and there is no contamination by intestinal bacteria.
- Class 2 are clean contaminated wounds, where the respiratory, digestive, or urinary tract is opened under controlled conditions and without unusual contamination. Examples include biliary and gastrointestinal surgery, although elective colorectal surgery is associated with a high infection rate of 9–25% [16].
- Class 3 wounds are contaminated, open, accidental wounds and surgical procedures where there is a large

degree of intestinal leakage, or incision of inflammatory tissues. Examples include penetrating abdominal trauma and surgery to resolve bowel obstructions.
- Class 4 are dirty wounds, where there is necrotic tissue or an abscess resulting from the delayed treatment of trauma, or a high degree of contamination due to intestinal perforation.

SSI is affected by the degree of initial bacterial contamination. Patients with Class 1 contamination are infected only by superficial skin bacteria, but those with Class 2 wounds, such as cases of colon surgery, may be contaminated by superficial skin bacteria, intestinal bacteria, or both. Surveillance for wound infection is required for 30 days after surgery, as strict monitoring and appropriate management can effectively reduce the wound infection rate. Wound infections are closely associated with morbidity and mortality, as well as medical costs and patient satisfaction. Therefore, the surgeon must take appropriate measures in accordance with the principles of infection control to prevent wound infection. In addition, appropriate prophylactic antibiotics should be used depending on the type of surgery; i.e., single-dose antibiotic treatment prior to surgery is recommended for Class 2, 3, and 4 wounds. While it is not necessary to administer prophylactic antibiotics for clean (Class 1) wounds, a single dose of prophylactic antibiotic should be administered prior to surgery to insert artificial devices.

Postoperative treatment of the wound also affects infection rates. In healthy patients, Class 1 and 2 wounds are sutured, but in contaminated cases the wound remains open for secondary or delayed primary suturing, as the infection rates of Class 3 and 4 wounds can range from 25% to 50%. Greater efforts have recently been made to reduce wound infection, and studies have shown that hyperglycemia has an adverse effect on leukocyte function [17]. The incidence of wound infection is also reported to be high in the presence of hyperglycemia in patients who have undergone several different operations. Therefore, it is important to maintain appropriate blood glucose levels after surgery [18, 19]. Studies have also shown that body temperature and oxygen levels are associated with wound infection, as hypothermia and hypoxia can increase the incidence of wound infection [20]. Although there is some variation in study results published to date, hypothermia and hypoxia should be avoided during surgery [21].

Incision wound infections can be effectively treated by incisional drainage without the need for antibiotic therapy. However, antibiotics should be administered in cases of severe cellulitis or systemic infection syndrome. The opened wound should be dressed twice a day while it heals naturally. Although local antibiotic administration and disinfection have been reported to be effective in uncontrolled complex infections, the value of this approach has not been established [22]. Although there are currently no prospective studies, vacuum-assisted suturing is recommended for large, complicated open wounds and can be used in areas where dressing is difficult [23]. Wound culture should also be considered as the incidence of infection with multidrug-resistant bacteria is increasingly common.

Intra-abdominal Infections

Contamination by peritoneal bacteria is referred to as peritonitis or intraperitoneal infection and is classified according to the cause. Primary bacterial peritonitis occurs when the peritoneal cavity (which is naturally aseptic) is infected from a remote location or invaded by direct infection and or peritoneal dialysis. These infections are caused by a single species of bacteria and require little surgical intervention; an appropriate antibiotic agent should be administered for 2–3 weeks. For the effective treatment of recurrent infections, it may be necessary to remove the peritoneal dialysis tube, peritoneal-venous perfusion device, or any similar devices.

Secondary bacterial peritonitis is caused by perforation of the intraperitoneal organs or by intraperitoneal contamination due to severe inflammation and infection (including appendicitis, perforation of the digestive tract, and diverticulitis). Effective treatment involves resection of the affected organs and removal of necrotic or infected tissue. Antibiotic agents appropriate for the treatment of aerobic and anaerobic bacteria should be administered [24], as most cases are difficult to diagnose prior to laparotomy and primarily result from colon perforations containing many bacterial strains. Once bowel movements return, oral therapy with a single or multiple wide-spectrum antibiotic can be implemented. In the absence of infection control, the mortality rate can exceed 40%, but controlling the source of infection and providing appropriate antibiotic therapy can reduce the mortality rate to 5–6% [25]. In recent years, the effectiveness of infectious disease control and appropriate antibiotic therapy has been approximately 70–90% [26]. Patients who fail to respond to standard therapy may progress to develop postoperative peritonitis or tertiary, persistent peritonitis due to a peritoneal abscess or gastrointestinal anastomotic leakage. Tertiary peritonitis has not yet been completely elucidated, but it is common in immunocompromised patients whose intraperitoneal immune system cannot effectively eliminate the initial secondary bacterial infection. Many types of bacteria or fungi (e.g., *Enterococcus faecalis, Enterococcus faecium, Staphylococcus epidermidis, Candida albicans*, and *Pseudomonas aeruginosa*) have been identified, with bacteria that do not respond to the initial antibiotic therapy being predominant. Unfortunately, despite appropriate antibiotic therapy, tertiary peritonitis is associated with a mortality rate of more than 50% [27]. In the past,

repeated surgery was required to manage intraperitoneal abscesses, but in recent years this approach has been replaced by percutaneous drainage, guided by abdominal ultrasonography or computed tomography. Surgical procedures should, therefore, be performed only in patients with multiple abscesses or abscesses in close proximity to critical organs (where percutaneous drainage is associated with a high level of risk) and in patients with persistent infections, such as intestinal leaks. The precise guidelines for antibiotic treatment and the duration of percutaneous drainage have not yet been established, but the short-term use of antibiotics (3–7 days) is appropriate when the presence of aerobic and anaerobic bacteria is suspected. Percutaneous drainage is usually maintained until intraperitoneal infection is relieved, the drainage volume is ≤10–20 mL/day, or there is no evidence of infection and the patient's condition improves.

Specific Organ Infection

Liver abscess is a rare condition; suppurative abscesses account for approximately 80% of cases, and the remaining 20% are caused by parasitic or fungal abscesses [28]. In the past, suppurative liver abscesses were often caused by pylephlebitis as a result of untreated appendicitis or diverticulitis, but cases now more commonly occur following manipulation of the bile ducts during the treatment of various diseases. For small, multiple abscesses, antibiotic treatment is continued for 4–6 weeks. In larger abscesses, a percutaneous drain should be inserted, and antibiotic treatment and drain removal should be implemented in accordance with general practice. Splenic abscesses are rare and should be treated in a similar way. Recurrent liver or splenic abscesses may require surgery; liver abscesses are treated by deroofing and marsupialization and splenic abscess by splenectomy. Secondary pancreatic infections (such as infected pancreatic necrosis or pancreatic abscesses) may develop into severe hemorrhagic pancreatitis, which is usually diagnosed by contrast computed tomography. Treatment includes antibiotic therapy and debridement of necrotic tissues when necessary [29]. Recently, minimally invasive procedures have also been attempted [30–32].

Infection of the Skin and Soft Tissues

These infections can be classified according to the requirement for surgical intervention. For example, infections of the skin or cutaneous structures (such as cellulitis and lymphadenitis) should be localized, but antibiotics alone can be effective; agents that are effective against Gram-positive bacteria are generally used. Swellings or boils may drain spontaneously but sometimes require incision drainage. Antibiotics should be used in cases where significant cellulitis occurs or when the cellulitis does not rapidly improve after surgical drainage. Rapidly progressive soft tissue infections are rare and difficult to diagnose and require immediate surgical treatment and antibiotic therapy. If appropriate incision drainage and antibiotic treatment is not successful, community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) infection should be suspected. In these cases, more drastic surgical incision drainage and antibiotic replacement should be implemented. Severe soft tissue infections (such as gangrene and necrotizing fasciitis) that are unresponsive to incisional drainage and antibiotic therapy are rare and are associated with a very high level of mortality (80–100%). Even when cases are detected and treated early, the mortality rate remains high, at 16–24% [33]. Patients with a deficient blood supply to the fascia, such as the elderly, immunosuppressed, or diabetic, or those with peripheral vascular disease, are at particular risk of this type of infection.

Nosocomial Infection After Surgery

Surgical patients are susceptible to a variety of hospital infections, including postoperative wound infection, urinary tract infections, pneumonia, and bacteremia. Patients requiring long-term mechanical ventilation are at greater risk of developing pneumonia, and infection is common in patients requiring intravenous infusion. Because of the complexity of many surgical procedures, the requirement for intravascular catheters for physiological monitoring, intravascular devices, drug administration, and parenteral nutrition has increased. However, the use of prophylactic antibiotics or antifungal agents is not effective and is contraindicated. Intravenous catheter infections are often difficult to detect as they may not be accompanied by any symptoms other than leukocytosis or the detection of bacteria in blood collected from peripheral blood vessels or catheter blood cultures. The catheter should be removed if a purulent substance is evident or in cases of severe bacteremia or fungal infection.

Sepsis

Sepsis consists of infection and an accompanying host response; it can manifest as sepsis, severe sepsis, or septic shock. Sepsis patients require systemic treatment, such as immediate resuscitation, antibiotic therapy, and removal of the cause of infection [6]. Early empirical broad-spectrum antibiotics are required for the treatment of patients with severe sepsis or hospital infections [34].

Enhanced Recovery After Surgery

Enhanced recovery after surgery (ERAS) programs ensure the optimal recovery of patients following surgery [35, 36]. The components include preoperative counseling, avoidance

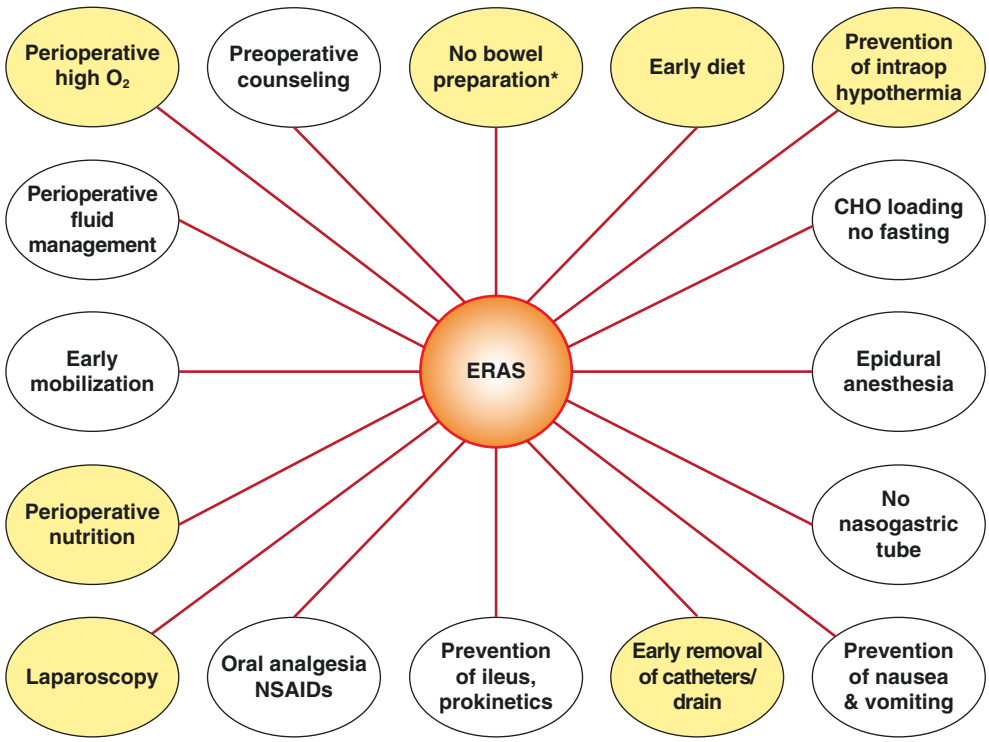

Fig. 28.2 ERAS components related to prevention of surgical site infection (highlighted in yellow). ∗ Note: Oral antibiotic preparation may reduce SSIs

of mechanical bowel preparation, supply of perioperative oxygen, perioperative fluid management, early patient mobilization, perioperative nutrition, oral analgesia, prevention of ileus, prevention of nausea and vomiting, avoidance of nasogastric tubes, carbohydrate loading and reduced starvation, prevention of intraoperative hypothermia, early nutrition, epidural anesthesia, early removal of catheters and drains, and the use of laparoscopy procedures (Fig. 28.2) [37, 38].

Preoperative mechanical bowel preparation has traditionally been performed to prevent postoperative complications and infection in patients undergoing abdominal procedures, as the reduction of fecal contact at the anastomotic site was considered to reduce complications (such as anastomosis leakage) and to reduce the possibility of fecal contamination if anastomotic leakage occurred. However, since the 1990s, many randomized comparative studies of patients with colorectal cancer have shown that preoperative bowel preparation does not prevent infection or anastomotic complications [39]. In contrast, oral antibiotics preparation may reduce SSI rates in patients undergoing colorectal surgery [40].

It is well-known that hypothermia during surgery increases infection complications and increases surgical stress caused by sympathetic hyperactivity. Several randomized studies have demonstrated that maintaining normal body temperature during surgery reduces the risk of infection after surgery [41, 42].

The benefit of providing additional oxygen during surgery to prevent infection remains controversial [20, 43], although a meta-analysis has shown the benefits of oxygen supplementation to reduce the incidence of SSI [44, 45]. In the ischemic environment, the surgical incision is vulnerable to bacterial invasion, and it is also assumed that oxygen has a direct antimicrobial effect [46].

The incidence of SSI is decreased with laparoscopic surgery as the small wound size, decreased use of electrocautery in the abdominal wall, and reduced stress response can effectively minimize SSI [47, 48].

Nutritional support is an important aspect of patient recovery after surgery. However, due to the complications associated with central intravenous feeding, parenteral nutrition may provide no benefit over fasting. By contrast, early enteral nutrition, within 48 hours of surgery or as soon as the gut is functioning, has been shown to be beneficial in the prevention of SSI [49].

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Thromboprophylaxis

29

Ben Morrison, Leigh Kelliher, and Chris Jones

Introduction

Comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), venous thromboembolism (VTE) is among the most common complications of hospital admission worldwide, causing significant morbidity and mortality [1]. It is estimated that VTE is responsible for around 10% of all hospital-related deaths [2], and while there are multiple factors that increase an individual's risk of developing VTE, one of the most important is undergoing major surgery [3]. Following surgery, part of the physiological response is to induce a prothrombotic state, and, when combined with a reduction in mobility and potential fluid shifts resulting in hemoconcentration, it is easy to see how VTE formation may be facilitated. In addition, both the type of surgery and indication (such as malignancy) will contribute to the overall risk of VTE. Without prophylaxis the incidence of VTE may rise to 40% following general surgery and be as high as 60% after major orthopedic surgery [4]. Despite the high incidence and associated risks, VTE is largely preventable [1], and numerous guidelines for thromboprophylaxis have been developed for a plethora of circumstances, including for specific surgical procedures. This chapter will explore the impact of VTE on patients, look at risk assessment and available treatments, and review the current evidence-based recommendations for thromboprophylaxis, including current ERAS® Society guidelines.

Epidemiology and Risk Factors

The incidence of VTE varies worldwide, with certain ethnic groups being less susceptible. Among people of European ancestry, the incidence ranges from 104 to 183 per 100,000 person-years; however, the incidence is higher in Afro-Caribbean and lower in Asian and Native American populations [5]. Table 29.1 lists risk factors for VTE based upon the United Kingdom's Department of Health risk assessment tool [6].

The incidence of VTE increases markedly over the age of 60 years. Gender also plays a role, with VTE more likely in men than women over the age of 50 [3]. Overall age-adjusted incidence is slightly higher for men at 130 per 100,000 person-years compared with 110 for women [3]. The proportion of pulmonary embolism (PE) to deep vein thrombosis (DVT) also increases with age, leading to a subsequent increase in VTE-related mortality [3].

Risk factors for VTE are cumulative, with an individual's risk of VTE greatly increasing in the presence of multiple factors. Patients who are hospitalized often have pre-existing risk factors, such as malignancy or obesity, combined with the event precipitating hospital admission such as trauma or pneumonia, thus illustrating the importance of individual patient VTE risk assessment upon admission and throughout their hospital stay [7].

Surgery is itself a major risk factor for VTE—an association that has long been recognized. The inherent nature of surgery, especially when it involves general anesthesia, can trigger all three elements of Virchow's triad, which describes three broad categories related to the formation of thrombus: *venous stasis*, as a result of reduced mobility perioperatively; *hypercoagulability*, as part of the body's response to surgical trauma; and *endothelial injury*, an unavoidable consequence of performing a surgical procedure (Fig. 29.1). The risk is further increased in patients undergoing surgery involving the pelvis or lower limbs, procedures with a total anesthetic time greater than 90 minutes (or 60 minutes for pelvic/lower limb surgery), procedures likely to reduce mobility postoperatively, patients requiring critical care perioperatively, and those with malignant disease.

VTE associated with malignancy has been described for over a century and is thought to account for approximately 20% of the total number of VTE cases [8]. The causes for

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Table 29.1 United Kingdom Department of Health venous thromboembolism (VTE) and bleeding risk factors [6]

Risk factors for VTE
Patient related
Active cancer or cancer treatment
Age over 60 years
Dehydration
Known thrombophilia
Obesity (BMI > 30 kg/m^2)
One or more significant comorbidities (e.g., heart disease; metabolic, endocrine, or respiratory pathologies; acute infectious diseases; inflammatory conditions)
Personal history or first-degree relative history of VTE
Use of HRT
Use of estrogen-containing contraceptive therapy
Use of thalidomide or its analogues
Varicose veins with phlebitis
Pregnancy or less than 6 weeks postpartum
Admission related
Acute surgical admission with inflammatory or intra-abdominal condition
Critical care admission
Significantly reduced mobility for 3 days or more
Hip fracture
Surgery involving pelvis or lower limb with a total anesthetic and surgical time of more than 60 minutes
Surgery with significant reduction in mobility
Total anesthetic and surgery time of more than 90 minutes
Risk factors for bleeding
Patient related
Active bleeding
Thrombocytopenia (platelets less than 75 × 10^9/l)
Hemato-oncology patients expected to become thrombocytopenic (platelets less than 75 × 10^9/l) within 7 days of admission
Acquired bleeding disorders such as acute liver failure
Concurrent use of anticoagulants known to increase the risk of bleeding (such as warfarin with an INR > 2)
Lumbar puncture/epidural/spinal anesthesia within the previous 4 hours or expected within the next 12 hours
Acute stroke
Uncontrolled systolic hypertension (> 230/120 mm Hg)
Untreated inherited bleeding disorders (such as hemophilia or von Willebrand's disease)
Admission related
Lumbar puncture/epidural/spinal anesthesia expected within the next 12 hours
Lumbar puncture/epidural/spinal anesthesia within the previous 4 hours
Neurosurgery, spinal surgery, or eye surgery
Other procedures with high bleeding risk

HRT hormone replacement therapy, *INR* international normalized ratio

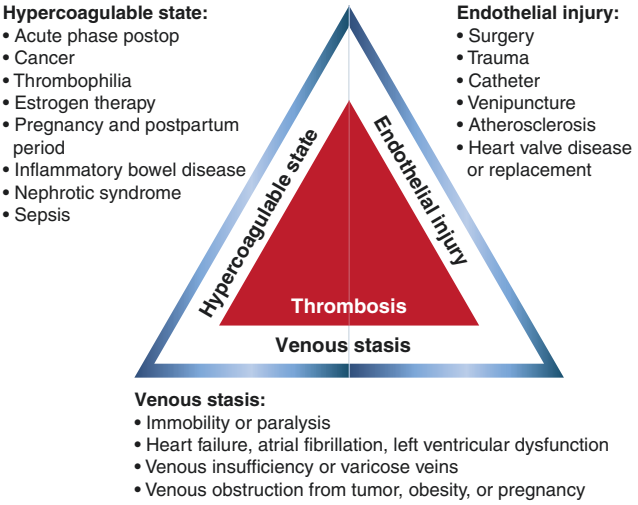

Fig. 29.1 Virchow's triad describing three broad categories related to the formation of thrombus

this are multifactorial, but again encompass all three elements of Virchow's triad. Macroscopically, tumors can compress blood vessels, creating venous congestion and stasis. Microscopically, tumors can stimulate a host response including the production of prothrombotic factors alongside factors inducing inflammation and necrosis [9]. Cancer treatments, such as chemotherapy and radiotherapy, can also promote a prothrombotic state. Cell-to-cell interactions resulting from tumor growth and spread may result in endothelial injury, thereby completing the triad [10]. The presence of cancer results in a hospitalized patient being twice as likely to develop a PE than those admitted with nonmalignant conditions [11]. The relationship between cancer and VTE has been known to help in the diagnosis of previously undiscovered malignancy in patients with presumed idiopathic VTE.

Obesity is an important modifiable risk factor for VTE, with risk increasing by as much as threefold for both men and women, with women of a body mass index (BMI) greater than 29 kg/m^2 having a relative risk for PE of 2.9 [12]. This is thought to be more as a result of the physical aspects of obesity promoting restricted mobility and impaired venous return as opposed to increases in coagulation factors per se, which themselves have not been found to be elevated in patients with a high BMI [13]. These patients are also particularly vulnerable in the presence of other risk factors, for example, the concurrent use of the oral contraceptive pill or hormone replacement therapy (HRT) [14].

Complications of Venous Thromboembolism

The risk of death from VTE is significant, with the 30-day mortality rate for DVT estimated at 6% and 10% for PE [15]. The true mortality rate for PE may be even higher with some postmortem studies demonstrating PE in 30% of subjects [15]. Mortality is also increased in patients with VTE related to malignant disease [16].

VTE can be a chronic condition, with an annual recurrence rate estimated at 5–7%, and the risk of recurrence is higher in patients with VTE related to cancer, old age, male gender, and obesity [17, 18].

Post-thrombotic syndrome is a common and potentially debilitating consequence of VTE occurring in 20–50% of patients following a DVT. Symptoms are similar to the initial DVT itself, including swelling, pain, and redness, and can progress to skin problems such as dryness and venous ulceration [19, 20].

Prevention of Venous Thromboembolism

Risk Assessment

Risk assessment is a vital part of ensuring patients receive the appropriate VTE prophylaxis. Risk factors are shown in Table 29.1 [6]. In the perioperative setting, the risk of VTE must always be balanced against the risk of bleeding. In January 2010 the National Institute for Clinical Excellence (NICE) in the United Kingdom published guidance on VTE prevention, which included risk assessment of all patients being admitted to hospital [6]. This initiative has seen an increase in patients being risk assessed from fewer than 50% in 2010 to more than 95% 5 years later. In doing so there is strong evidence that incidence and mortality from VTE for hospital inpatients have decreased significantly [21, 22]. The UK Department of Health produced a risk assessment tool, which includes factors that put patients at a higher risk of developing VTE and factors putting them at risk of bleeding [6].

This risk assessment tool has also been extrapolated for use as a means to identify any patients with contraindications to the various methods of thromboprophylaxis available, aiding those undertaking the assessment and subsequent prescription to make safe and appropriate decisions.

Thromboprophylaxis

Thromboprophylaxis can be broadly divided into pharmacological and non-pharmacological treatments. This gives healthcare practitioners a broader range of treatments to offer in the context of several factors that may preclude patients from certain forms of prophylaxis, such as those at a higher risk of bleeding or with pre-existing lower limb conditions.

Non-pharmacological Treatments

The mainstay of mechanical prophylaxis is in the form of compression stockings (thromboembolism-deterrent [TED] stockings), which are designed to produce graduated compression of the leg with an ideal pressure of 14–15 mm Hg around the calf. It is believed that the use of bandages to compress the legs for the purpose of reducing blood pooling has been in practice in various cultures for centuries, even millennia, with descriptions of fighters wearing leg bandages appearing in various anthropological artifacts dating as far back as 5000 BCE [23]. Modern medical application of compression stockings, specifically for VTE prophylaxis, started around the late nineteenth century along with improved manufacturing methods [24].

The mechanisms of action of compression stockings include reducing the cross-sectional area of veins through compression, thus increasing blood flow velocity and preventing venous stasis; increasing the efficacy of the calf muscles acting as a pump, helping to improve valve function and further prevent venous pooling; and finally a modulation of the levels of certain clotting factors in the venous circulation [25]. Patients must wear the correct size as decided by up-to-date leg measurement and should be shown how to wear the stockings correctly to reduce the risk of potentially serious complications such as blistering or venous outflow obstruction. Indeed, if positioned incorrectly they can increase the risk of developing a DVT. Stockings should be worn until the patient is able to mobilize sufficiently, and they should be removed at least once a day for hygiene purposes and in order for the skin beneath to be inspected. If patients develop lower limb edema, stockings should be resized appropriately or discontinued with an alternative means of thromboprophylaxis being instituted in their place. Contraindications to compression stockings are:

- Suspected or proven peripheral arterial disease
- Peripheral arterial bypass grafting
- Peripheral neuropathy or other causes of sensory impairment
- Any local conditions in which anti-embolism stockings may cause damage; for example, fragile “tissue paper” skin, dermatitis, gangrene, or recent skin graft
- Known allergy to material of manufacture
- Severe leg edema
- Major limb deformity or unusual leg size or shape preventing correct fit

If stockings are not suitable, then intermittent pneumatic compression devices should be worn as an alternative. These can be more limiting for patients, however, as they require connection to a pneumatic device and thus are not inherently portable. They work through repeated, intermittent inflation and deflation of one or more cuffs of air positioned around the calf aiming to compress deep veins and encourage proximal blood flow. Veins refill from the distal circulation upon deflation of the cuffs, which helps to stimulate and maintain a pulsatile blood flow.

Both stockings and pneumatic devices can be worn intraoperatively and simultaneously. It is important to be especially vigilant of pressure areas where these devices are worn and aware of how certain patient positions, especially during prolonged procedures, can put them at higher risk intraoperatively of complications such as compartment syndrome [26,

27]. Compression devices can work synergistically with pharmacological thromboprophylaxis to further reduce the risk of VTE [28].

Regardless of the methods of VTE prophylaxis employed, early postoperative mobilization remains vital to helping prevent thrombus formation. Enhanced recovery after surgery (ERAS) principles are geared toward allowing patients to sit out of bed and mobilize at the earliest opportunity conferring a number of benefits. Mobilization results in improved venous blood flow from the lower limbs, reducing venous stasis and thus a reduced risk of VTE. Methods of mobilization can be employed that do not require patients to leave their hospital beds. These include pedaling systems placed at the foot of the bed allowing alert but restricted patients to engage with physiotherapy regimens. Once used to such a system, the patient does not necessarily require assistance in order to undertake exercise, thus helping them to independently regain limb strength while protecting themselves from VTE.

Pharmacological Treatments

Unfractionated Heparin and the Low-Molecular-Weight Heparins

Unfractionated heparin (UFH) mediates its anticoagulant effect via inducing antithrombin III to inhibit factor Xa and thrombin—both key proteases required for thrombus formation (Fig. 29.2). It is most commonly used for the treatment of VTE with its role in prevention of VTE limited by the fact that it must be given intravenously as an infusion and monitored with serial activated partial thromboplastin times (aPTT). In practice this usually means that UFH can only be administered in inpatients and for short time periods, making it a suitable option for perioperative "bridging" anticoagulation in those patients who are at high risk of VTE. A further advantage of UFH in this setting is that its effects can be acutely reversed through administration of protamine.

The low-molecular-weight heparins (LMWHs) (e.g., enoxaparin, dalteparin, tinzaparin) are derivatives of UFH obtained by fractionation of polymeric heparin to yield molecules with an average molecular weight of less than 8000 Da. They also produce their anticoagulant effect via inhibition of factor Xa, but not thrombin. They are among the commonest agents used for prevention of VTE as they may be given subcutaneously, do not require aPTT monitoring, and have more predictable pharmacokinetics than UFH. They form a standard of care in many thromboprophylaxis guidelines across the world [6, 29, 30]. However, they are not without limitations, principally that they can accumulate in patients with renal impairment and increase the risk of bleeding—a problem compounded by the fact that, unlike UFH, LMWHs are not completely reversed by protamine. Both UFH and LMWH can cause heparin-induced thrombocytopenia (HIT) and are contraindicated patients with a history of this.

Heparin Alternatives

Used widely for VTE prophylaxis in orthopedic surgery and elsewhere, fondaparinux is a factor Xa inhibitor related to heparin (Fig. 29.2). Like the LMWHs it can be administered subcutaneously and has predictable pharmacokinetics, but it has the advantage that it does not cause HIT. However, there is no specific reversal agent for fondaparinux, and its major risk is bleeding, especially in patients with renal impairment.

Danaparoid is a low-molecular-weight heparinoid that is chemically distinct from heparin that works by inhibition of both factor Xa and to a lesser degree thrombin. It has been used widely for VTE prophylaxis in orthopedic surgery and is suitable for use as an alternative to LMWH in patients with HIT. There is no specific reversal agent for danaparoid, and the bleeding risk is increased in patients with hepatic or renal dysfunction.

Antiplatelet Agents

Antiplatelet agents (APA) such as aspirin, clopidogrel, and dipyridamole are commonly used for the prevention of cardiovascular thrombotic events. While their mechanisms of action are different, aspirin irreversibly inhibits the enzyme cyclooxygenase (COX) and, thus, the production of thromboxane; clopidogrel is an adenosine diphosphate (ADP) receptor antagonist; dipyridamole is an adenosine reuptake inhibitor—the end result is the same: inhibition of platelet function. The role of APA as sole agents in VTE prophylaxis is controversial, with evidence suggesting they are less effective than LMWH and may have little or no benefit [31]. The combination of LMWH and APA, while effective for VTE prophylaxis, increases bleeding risk and current European, UK, and US guidelines all recommend that in patients already taking an APA the risk of bleeding must be balanced against the risk of arterial thrombosis before withholding these drugs. If the risk of VTE outweighs the risk of bleeding, then pharmacological VTE prophylaxis may be used. If the risk of bleeding is greater than the risk of VTE, then mechanical VTE prophylaxis should be considered [6, 30, 32].

Coumarins

These drugs are oral anticoagulants that work by inhibiting the enzyme vitamin KO reductase. This leads to a reduction in the function of clotting factors II, VII, IX and X which depend on vitamin K for activation (Fig. 29.2). The principal drug in this class is warfarin, which has long been used for the treatment and prevention of thrombus formation in a variety of settings. Dosing of warfarin can be difficult as it has many interactions with other drugs and some foods that can lead to large fluctuations in its efficacy. Regular blood monitoring of

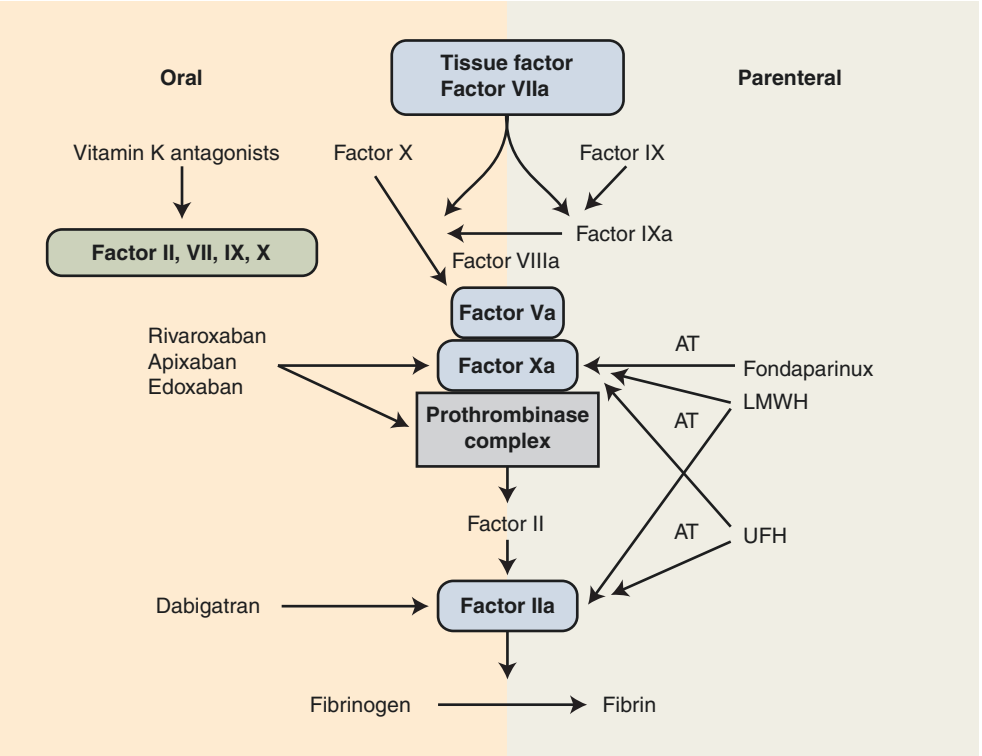

Fig. 29.2 Coagulation cascade showing drugs used to intervene at different stages. AT antithrombin promoter, LMWH low-molecular weight heparin, UFH unfractionated heparin

the international normalized ratio (INR) and appropriate dose adjustments are essential to maintain treatment within the therapeutic range. Warfarin therapy is effective VTE prophylaxis and is used in some centers, particularly in the United States, for extended thromboprophylaxis following major orthopedic surgery [33]. However, the described problems with dosing and blood monitoring mean it does not feature in ERAS® Society, UK, or European guidelines [6, 29, 34].

Direct Oral Anticoagulants

Formerly termed the "novel oral anticoagulants" (NOACs), the direct oral anticoagulants (DOACs) are a group of new agents that are licensed internationally for DVT prophylaxis following lower limb arthroplasty. They include apixaban, rivaroxaban, and edoxaban, which all act via direct inhibition of factor Xa and dabigatran, which inhibits thrombin (Fig. 29.2). They are an attractive option for VTE prophylaxis as they can be given orally, do not require therapeutic monitoring, and have reliable pharmacokinetics making dosing relatively simple. However, with the exception of dabigatran, they do not have specific antidotes, and their actions are terminated principally by renal clearance. This limits their usage in patients with renal impairment and also presents a problem in the context of major postoperative bleeding. As mentioned, dabigatran is the exception and may be reversed with the recently licensed specific monoclonal antibody idarucizumab. At present DOACs are only licensed for VTE prophylaxis following orthopedic surgery, but as further reversal agents are developed and evidence accumulates, their use may well be extended to cover other types of surgery.

Patients Already Anticoagulated

Patients already on anticoagulation treatment may require so-called "bridging" therapy perioperatively. This is the planned cessation of regular treatment and conversion to a shorter-acting alternative, the most common example being withholding warfarin therapy and converting to heparin perioperatively, usually for 10–12 days. There remains controversy as to the safest method of managing anticoagulant therapy perioperatively in patients who are, by definition, at high risk of VTE (hence the need for long-term anticoagulation) but who may also be at significant risk of bleeding from the operation, if anticoagulation is not reversed/suspended appropriately. Historically it was felt necessary to use some form of bridging in all patients receiving anticoagulants; however, patients receive anticoagulation for a variety of indications, and the risk of thrombosis if anticoagulation is suspended varies dependent on a variety of factors. Recent studies have suggested that major bleeding is significantly more prevalent in patients receiving bridging therapy, and there is no decrease in thrombotic events for patients who would otherwise be considered low risk [35–38]. The decision on whether or not bridging therapy is appropriate should be made on an individual basis after assessing and balancing all risk factors including the origi-

nal indication for anticoagulation, e.g., AF; pre-existing risk factors, e.g., thrombophilias; and the nature of surgery, in particular procedures with a higher bleeding risk or where bleeding can have more serious consequences. Many institutions now have their own guidelines regarding bridging therapy, and hematology specialist opinion should be sought where doubt remains.

Separate guidance exists for patients receiving anticoagulation following cardiac interventions such as drug-eluting coronary artery stent insertion. In the elective setting, surgery should be postponed until after dual antiplatelet therapy (usually aspirin and a thienopyridine such as clopidogrel) is complete, currently 6 weeks with bare-metal stents and 6 months with drug-eluting stents. If surgery cannot be postponed, dual antiplatelet therapy should be continued throughout the perioperative period unless under direct instruction of a cardiologist. For patients who are at a high risk for cardiac events but do not have coronary stents in situ, aspirin should be continued perioperatively, but thienopyridines should be stopped 5 days preoperatively and recommenced 24 hours postoperatively assuming adequate hemostasis is achieved. Patients taking antiplatelets who are low risk for cardiac events should stop antiplatelet therapy 7–10 days preoperatively [35]. A new generation of drug-eluting stents is becoming more commonplace and may not require as long a period of dual antiplatelet therapy. Cardiology opinion should be sought where there is any doubt.

When to stop current anticoagulation therapy is dependent upon the treatment being prescribed. Warfarin should be stopped at least 5 days preoperatively and INR checked in sufficient time (ideally 1–2 days) before surgery in order to take any necessary steps to further reduce the INR before surgery to ensure it is within acceptable limits (usually below 1.5). If INR remains high 1–2 days preoperatively, low-dose oral vitamin K may be considered to reverse the effect of warfarin. Where the INR remains elevated, and surgery cannot be postponed, further reversal therapies can be considered; these include intravenous (IV) vitamin K, fresh frozen plasma, or prothrombin complex concentrate. While effective at normalizing the INR, administration of these therapies may result in difficulty in restoring a consistently therapeutic INR with warfarin postoperatively. The reinstitution of anticoagulant therapy will always depend on the surgical procedure and the risk of bleeding vs. the risk of thrombosis, but in general patients at low risk of VTE can usually restart their warfarin the day after surgery. High-risk patients who have received bridging should resume therapeutic heparin 48–72 hours postoperatively in addition to their warfarin. The bridging therapy can be stopped once the INR has returned to within the required therapeutic range.

Different antiplatelet agents vary in their therapeutic half-life and thus require different perioperative regimens. Most inhibit platelet function irreversibly, requiring the production of new platelets to terminate their effect. This typically takes 7–10 days, meaning these antiplatelets need to be stopped 7–10 days preoperatively [35]. Perhaps the most common antiplatelet agent in use is aspirin; however, its antiplatelet effect is relatively weak compared with some other agents meaning it is often safe to continue throughout the perioperative period. As always, this decision should be made on a risk/benefit basis. For the same reason, aspirin need not be withheld prior to regional or neuraxial blockade, as is also the case with antiplatelet drugs with reversible platelet inhibition such as dipyridamole [39].

When to stop heparins depends upon whether LMWH or UFH is being administered and the intended effect, be it prophylactic or therapeutic. UFH should be stopped 4–6 hours preoperatively, and the activated partial thromboplastin time (aPTT) can be measured to ensure the anticoagulant effect has dropped sufficiently. Prophylactic and therapeutic subcutaneous LMWH should be stopped 12 hours and 24 hours before surgery, respectively [35]. After performing a regional nerve block or removing an epidural catheter, further doses of UFH should not be given until at least 1 hour postoperatively for subcutaneous, at least 4 hours for LMWH medications [39] with other guidelines suggesting even longer time periods of up to 12 hours [35].

DOAC medications also vary as to timing of cessation preoperatively. As mentioned previously, only dabigatran has a currently available reversal agent; thus care must be taken to ensure these drugs have been stopped in sufficient time. For regional or neuraxial blockade, timings for stopping these drugs vary considerably depending upon which guidelines are followed. These times can also be affected by renal dysfunction [35, 39].

ERAS® Society Guidelines

The ERAS® Society has published a number of different specialty guidelines, which all include VTE prophylaxis. A summary of their VTE recommendations can be found in Table 29.2.

Some Specialties Currently Not Covered by ERAS® Society Guidelines

Orthopedic Surgery

Individual centers have been using their own ERAS protocols in both hip and knee arthroplasty for a number of years with some success [40], but to date no consensus guidelines exist. VTE prophylaxis is a key tenet of any successful ERAS pathway, especially in major orthopedic surgery where VTE risk is particularly high [4]. However, agreement over a universal approach in this setting has remained elusive.

Table 29.2 Summary of ERAS® Society venous thromboembolism (VTE) recommendations

Guideline	Section on VTE	Summary Recommendations	Heparin	TEDs	SCDs	Other Anticoagulants	Early mobilization	Other Comments	Level of evidence	Recommendation
Bariatrics	Yes	Thromboprophylaxis should involve mechanical and pharmacological measures with LMWH. Dosage and duration of treatment should be individualized	Once-daily LMWH recommended dosed according to BMI with higher doses showing no increased risk of bleeding; continue for 3–4 weeks	Recommended	Recommended	Stop vitamin K antagonists 5 days pre-op and resume 12–24 hours post-op with "bridging" LMWH	Recommended	IVC filters not recommended	Mechanical measures in combination with LMWH: high	Strong
Breast	Yes	Patients should be assessed for venous thromboembolism risk. Unless contraindicated, and balanced by the risk of bleeding, patients at a higher risk should receive low-molecular-weight heparin or unfractionated heparin until ambulatory or discharged. Mechanical methods should be added	Higher VTE risk patients should receive LMWH or UF heparin starting pre-op and continuing for at least 7–10 days, up to 4 weeks	Recommended	Recommended				Moderate	Strong
Colonic	Yes	Patients should wear well-fitting compression stockings, have intermittent pneumatic compression, and receive pharmacological prophylaxis with LMWH. Extended prophylaxis for 28 days should be given to patients with colorectal cancer	Once-daily LMWH or UF heparin extended to 28 days with colorectal cancer	Recommended	Recommended				Stockings, compression, LMVH, extended prophylaxis: high	Strong

Table 29.2 (continued)

Guideline	Section on VTE	Summary Recommendations	Heparin	TEDs	SCDs	Other Anticoagulants	Early mobilization	Other Comments	Level of evidence	Recommendation
GI surgery	No	N/A					Recommended	Mobilization mentioned in context of overall benefits	Prophylaxis: high	
Gastrectomy	Yes	LMWH reduces the risk of thromboembolic complications. Concomitant use of epidural analgesia necessitates close adherence to safety guidelines. Mechanical measures should probably be added for patients at high risk	LMWH started 2–12 hours pre-op continued for 4 weeks after discharge	High-risk patients	High-risk patients				High	Strong
Gyne-oncology	Yes	Patients at increased risk of VTE should receive dual mechanical prophylaxis and chemoprophylaxis with either low-molecular-weight heparin or unfractionated heparin. Prophylaxis should be initiated preoperatively and continued postoperatively. Extended chemoprophylaxis (28 days post-op) should be prescribed to patients who meet high-risk ACCP criteria, including patients with advanced ovarian cancer. Further studies on extended postoperative prophylaxis with direct-acting oral anticoagulants, and guidelines on VTE prophylaxis during ambulatory chemotherapy for gynecologic cancer, are needed	All gynecological oncology patients having major surgery lasting >30 min should receive LMWH or UF heparin starting pre-op and continued post-op	Recommended	Recommended				Heparin + mechanical: high; pre-op admin: moderate; extended prophylaxis with heparin: high; extended prophylaxis with DOAC: low	Pre-op DVT prophylaxis: strong; HRT: weak; extended prophylaxis: strong; DOAC prophylaxis: weak

Head and neck cancer surgery	Yes	Patients undergoing head and neck cancer surgery with free flap reconstruction are at increased risk of VTE and should undergo pharmacologic prophylaxis; however, the risk of bleeding must be weighed against the benefits on an individualized basis	VTE risk must be weighed against risk of bleeding on an individual basis			Concurrent antiplatelet therapy increases bleeding risk		No pharmacological methods have been shown to reduce risk of free flap anastomosis thrombosis or flap necrosis	High	Strong
Liver surgery	Yes	LMWH or unfragmented heparin reduces the risk of thromboembolic complications and should be started 2–12 h before surgery, particularly in major hepatectomy. Intermittent pneumatic compression stockings should be added to further decrease this risk	Continue use of heparin for 4 week following hospital discharge, particularly in oncology patients	Recommended	Recommended				Use of heparin: moderate; use of intermittent pneumatic compression devices: low	Use of heparin: strong; use of intermittent pneumatic compression devices: weak
Pancreatico-duodenectomy	Yes	LMWH reduces the risk of thromboembolic complications, and administration should be continued for 4 weeks after hospital discharge. Concomitant use of epidural analgesia necessitates close adherence to safety guidelines. Mechanical measures should probably be added for patients at high risk	LMWH preferred over UF heparin in view of compliance. Treatment started 2–12 hours preoperatively and continued at least until patient fully mobile	Moderate to high-risk patients	Moderate to high-risk patients				High	Strong

(continued)

Table 29.2 (continued)

Guideline	Section on VTE	Summary Recommendations	Heparin	TEDs	SCDs	Other Anticoagulants	Early mobilization	Other Comments	Level of evidence	Recommendation
Radical cystectomy	Yes	Patients should wear well-fitting compression stockings and receive pharmacological prophylaxis with LMWH. Extended prophylaxis for 4 weeks should be carried out in patients at risk. 12 h interval between injections and epidural manipulation. Cystectomy patients are considered at risk; prolonged prophylaxis should therefore be administered.	Evidence based-upon colorectal surgery, not specific to cystectomy. Recommends same principles applied including extended prophylaxis	Recommended	Recommended			Guidelines based on evidence for colorectal surgery	High	Strong
Rectal/pelvic surgery	Yes	Patients should wear well-fitting compression stockings and receive pharmacological prophylaxis with LMWH. Extended prophylaxis for 28 days should be considered in patients with colorectal cancer or other patients with increased risk of VTE	Continue heparin (LMWH recommended) for 4 weeks postoperatively even if early recovery or early discharge from hospital is achieved						High	Strong

Abbreviations: *LMWH* low-molecular-weight heparin, *BMI* body mass index, *IVC* inferior vena cava, *UF* unfractionated, *ACCP* American College of Chest Physicians, *DOAC* direct oral anticoagulant, *DVT* deep vein thrombosis, *HRT* hormone replacement therapy

In the United Kingdom, NICE recommends prophylaxis for 28 days following hip replacement and 14 days following knee replacement [6]. NICE suggests the individual clinician choose between one of three options for hip replacement:

- LMWH for 10 days followed by aspirin for a further 28 days
- LMWH for 28 days combined with thromboembolism-deterrent (TED) stockings until discharge
- Rivaroxaban for 5 weeks

They add that in cases where none of the above are favorable options, then either apixaban or dabigatran could be considered. Similarly, for knee replacement, they recommend one of the following:

- Aspirin for 14 days postoperatively
- LMWH for 14 days
- Rivaroxaban also for 14 days

Meanwhile, in the United States, there are two competing guidelines produced by two different colleges. The American College of Chest Physicians (ACCP) focuses on prophylaxis to prevent DVT and PE and suggests that the clinician choose one of the following pharmacological agents compared to no anticoagulation:

- LMWH
- A DOAC (either a direct thrombin inhibitor or factor Xa inhibitor)
- Low-dose UFH
- Warfarin
- Aspirin plus mechanical prophylaxis with an intermittent pneumatic compression device

They do, however, suggest the use of LMWH in preference to the other options and recommend a minimum of 10–14 days treatment, which can be extended to 35 days [30].

The American Academy of Orthopedic Surgeons (AAOS), however, says that the ACCP guidelines focus inappropriately on prophylaxis that is effective for prevention of DVT, as a surrogate for PE (their primary focus is to reduce the incidence of PE). They recommend, by consensus, the combined use of mechanical devices and pharmacological prophylaxis, but were unable to recommend one particular regimen [41].

In general, most current guidelines recommend some form of pharmacological prophylaxis for all patients undergoing hip and knee replacement. However, much of the evidence upon which these guidelines are based comes from the pre-ERAS era, and with the widespread adoption of ERAS programs promoting early postoperative mobilization, it may be revealed that routine pharmacological prophylaxis is only required in high-risk patient groups. Data from ERAS programs in Denmark have found that only giving in-hospital chemoprophylaxis for these patients has not led to higher rates of VTE in the community, and so for chemoprophylaxis continued at home, they now only target high-risk groups [42, 43]. This is likely to be backed up by the ERAS® Society in future guidelines. The Danish have similar guidelines for colorectal surgery and found—with a comprehensive ERAS program and VTE prophylaxis only while an inpatient—a 0.2% rate of nonfatal symptomatic VTE at 60 days, thus questioning the prolonged use of VTE prophylaxis [44].

Obstetrics

Analogous to the situation in orthopedic surgery, there are numerous published ERAS studies in this area utilizing a variety of different protocols but, at the time of writing, no consensus guidelines. Thrombosis and thromboembolism remain the leading cause of direct maternal death in the United Kingdom [45], and so effective preventative strategies are essential. The Royal College of Obstetricians and Gynaecologists from the United Kingdom published comprehensive guidelines in 2015 on VTE prophylaxis [46] in which they stated that all women should have documented assessment of risk factors (such as medical comorbidities, e.g., cancer and heart failure; age over 35; obesity; smoking; multiple pregnancy or lower-segment cesarean section [LSCS]). Individuals with four or more risk factors should be considered for LMWH throughout the antenatal period and for 6 weeks postnatally. Those with three risk factors should be considered for LMWH from 28 weeks, continuing for 6 weeks postnatally; and those with two risk factors receive LMWH for at least 10 days postpartum. Other individual risk factors carry specific guidance; e.g., patients with a BMI greater than 40 and those who required an emergency LSCS should both receive 10 days of LMWH postpartum.

The Future

As the newer anticoagulant medications become more established, the evidence for their benefits and risks will grow, and guidelines will likely change to follow reflect this. DOACs are becoming increasingly popular, particularly as an alternative to warfarin, which, although well-established as effective and safe, presents considerable practical and logistical challenges for both patients and health services. A number of trials comparing warfarin with DOACs have shown equivalent efficacy but with fewer complications in the DOAC group [47, 48]. Specific reversal agents for these drugs are on the horizon, with agents for the reversal of rivaroxaban and apixaban both currently undergoing phase III trials [49], which, if favorable, will increase their appeal to prescribers. Novel agents targeting other aspects of thrombus formation

are also in development, including drugs aimed at disrupting factors XI and XII. A trial has already taken place using one of these drugs in a perioperative setting demonstrating effective VTE prevention and safety with respect to risk of bleeding [50]. As these drugs become more widely prescribed and the evidence base grows, there may come a time when they can challenge LMWH as the primary pharmacological agent for perioperative thromboprophylaxis.

Conclusion

VTE is a common, life-threatening, and preventable perioperative complication. Effective and safe thromboprophylaxis is a fundamental standard of perioperative care and a key tenet of an ERAS program. All patients scheduled for surgery should be adequately risk assessed as early as possible preoperatively and reviewed following any significant events in the perioperative journey. The vital aspects of thromboprophylaxis are choice and timing of administration of pharmacological agents and consideration of non-pharmacological treatments including early mobilization. The choice of pharmacological agent is largely dependent upon other aspects of a patient's condition such as renal function or ability to absorb enterally. Timing is dependent upon the indication for and nature of surgery and must always consider safety in terms of perioperative bleeding risk and anesthetic/analgesic modality (e.g., neuraxial blockade/regional anesthesia). Patients with malignant disease or having lower limb orthopedic surgery are also likely to require prolonged thromboprophylaxis, at least until full mobility is restored, but with ERAS programs becoming more effective at restoring mobility, this could have an effect upon the duration of thromboprophylaxis. The introduction of new thromboprophylaxis agents is likely to change practice in the near future, and we must remain vigilant as to the nature and effects of these drugs in order to continue to safely manage patients while maintaining the lowest possible risk of VTE formation.

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Part VI

ERAS After Discharge

Functional Recovery at Home and After Discharge

30

Larissa Meyer and Pedro T. Ramirez

Introduction

Enhanced recovery after surgery (ERAS) programs are comprehensive and multidisciplinary care plans that integrate evidence-based interventions in the perioperative care of the patient. A number of guidelines have been published that describe the essential elements of an ERAS program [1, 2]. Compliance with such guidelines has been shown to improve perioperative outcomes [3]. One of the essential elements of a successful implementation of any ERAS program is the ability of a patient to not only recover physically from the surgical procedure but to also return to full functional capacity. In this chapter we aim to explore what functional recovery means and the complexity involved in defining and measuring recovery.

The recovery process is complex, and it often encompasses several dimensions of physical, emotional, economic, and social health. In addition, the definition of "recovery" may be different among those involved in the process [4]. To the patient, recovery may take weeks or months, and it generally equates with full return to normal daily activities. Patients often recover at different time frames for the various dimensions of functional recovery. For example, economic recovery and return to work may lag behind emotional or physical dimensions of recovery. However, additional research is needed within the diverse surgical populations to define and better understand the nuances of functional recovery from a patient's viewpoint.

Functional Recovery

Postoperative recovery has been described as following a specific pattern that starts with a rapid deterioration from baseline function in the immediate postoperative period and then gradually rehabilitates back to or surpasses the preoperative baseline [5]. This recovery trajectory is featured in the ERAS® logo (Fig. 30.1) and represents, in a pictorial sense, the benefit of enhanced recovery programs to a patient's functional recovery. The recovery trajectory will not be the same for all surgeries or patients. Some patients may not realistically achieve a full recovery to their preoperative baseline, and others may improve beyond their preoperative baseline. In addition, one must also consider that the postoperative recovery for patients with cancer may be further impacted by the side effect profile of the adjuvant therapy—either chemotherapy, other systemic treatments, or radiation.

The impact of a faster physical and functional postoperative recovery, as generally noted in ERAS programs, is of paramount importance in the setting of cancer patients. After cancer surgery, either complications or subsequent disability from such complications may prevent or delay patients from receiving subsequent adjuvant therapy. A number of centers have evaluated the principle known as RIOT (return to intended oncologic treatment). RIOT has two components: first, a binary outcome (whether the patient did or did not initiate intended oncologic therapies after surgery), and, second,

Fig. 30.1 The bottom arrow represents functional recovery after surgery without participation in an enhanced recovery after surgery (ERAS) program, and the top arrow graphically demonstrates the benefits of enhanced recovery after surgery with less of an impact on function and a quicker recovery

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the time between surgery and the initiation of such therapies. In a study by Aloia and colleagues [6] from MD Anderson Cancer Center, the investigators evaluated 223 patients with liver tumors who underwent open hepatectomy and 27 patients who had the same procedure by minimally invasive surgery (MIS). They found that 75% of patients were able to return to planned oncologic therapy and that inability to RIOT correlated with shorter disease-free and overall survival. This study proposed that efforts should be made to speed the recovery process for patients undergoing cancer surgery in order to decrease any compromise on oncologic outcomes. The same group then performed an evaluation of this same principle after initiation of an ERAS program and noted that after introduction of such program, there was an improvement in RIOT to 95% [7]. In cancer patients, it is imperative to focus on developing strategies that not only reduce patient disability but also maintain adequate functional capacity.

In a recent review by Bowyer and colleagues, [8] the authors evaluated the scope and measurement of postoperative quality of recovery. They proposed that there are three phases of recovery: an early, intermediate, and late phase. In the early phase, one needs to consider factors that are essential for hospital discharge, such as physiologic stability, pain, nausea, and gastrointestinal function. The intermediate phase is the time during the first weeks after surgery, where nociceptive, emotional, functional, and cognitive recovery are most crucial. Lastly, the late phase of recovery is that which is more than 6 weeks after surgery; and this is where elements such as persistent pain, nausea, and declining cognitive capacity play a greater role.

Patient-Reported Outcomes

Length of stay in the hospital has declined in the ERAS era. As such, the majority of recovery after surgery occurs outside of the hospital environment, either in a nursing or rehabilitation facility or, more often, in the home environment. Thus, recovery outside of the hospital typically encompasses the late phase of recovery. Patients and caregivers can feel vulnerable after discharge and underprepared to carry on the recovery process at home [9, 10]. Patients with ostomies may be particularly vulnerable. In one study of patients who underwent cardiac surgery, a common theme that emerged was the sentiment that discharge felt akin to being "thrown to the wolves" [10]. There continues to be a knowledge gap of how medical care teams can better support patients and their caregivers to optimize functional recovery at home. Studies involving multiple stakeholders including patients, family members, surgeons, and other medical caregivers suggest that utilizing information and communication technology for multimedia and education initiatives would be welcomed by patients and families [11, 12]. Preliminary pilot studies demonstrate feasibility from telemedicine, multimedia education, and follow-up support in terms of knowledge, quality of life, and acceptance from patients and caregivers [13, 14]. Apps designed to assist with communication about distressing symptoms and that provide education support and self-help advice may also be helpful during the out-of-hospital recovery phase [15, 16]. For example, interactive patient-reported outcomes (PRO) apps can help provide recovery reminders (ambulate, nutrition, wound care) or provide severity tailored feedback for self-management and guides on when to reach out to their surgical team.

One of the greater challenges in measuring recovery is that there is no single outcome that completely captures the results of implementation and success of an ERAS program and, more specifically, functional recovery after surgery. While there are similarities in the process of surgical recovery, there are also important differences and challenges based on the specific patient population or procedure. Even within a single surgical specialty, such as orthopedic surgery, specific functional recovery outcomes and how they are best measured will vary for patients undergoing different procedures, such as ankle replacement surgery, spine surgery, or hip replacement [17–19]. Not only may the selection of outcome measures differ by patient population or surgical procedure, but outcome measures may also vary according to where the patient lies in the different phases of recovery. While the surgeon and healthcare team can provide outcome measures based on surgical and physical complications, it is crucial to obtain measures, such as patient-reported outcomes, where the measure may be prioritized by the stakeholders and for a particular health condition or treatment [20]. Such PROs can be determined directly by the patient using validated scales or health profiles.

Lee et al. proposed a specific set of measures targeting each phase of recovery (Table 30.1) [4]. In this algorithm, although there are numerable examples of assessment tools, they proposed measuring the early phase of recovery, by focusing on physiologic and biologic outcomes and that one tool that captures such information is the Aldrete postanesthetic recovery score [21]. In assessing the outcomes of the intermediate phase of recovery where symptoms and impairment in activities of daily living are most crucial, the authors recommended the quality of recovery score [22]. This tool encompasses five dimensions of recovery (emotional state, physical comfort, psychological support, physical independence, and pain). Another alternative for abdominal surgeries is the Abdominal Surgery Impact Scale [23]. Lastly, in assessing the late phase of recovery, the authors suggested a number of tools that evaluate function and health-related quality of life. These include the 6-minute walk test [24], the Community Health Activities Model Program for Seniors (CHAMPS) questionnaire, [25] and the Short Form 6-D

Table 30.1 Stages of recovery

Phase of recovery	Definition	Time frame	Threshold	Outcomes	Examples of existing instruments
Early	From OR to discharge from PACU	Hours	Safety (sufficiently recovered from anesthesia and safe to go to floor)	Physiologic and biologic	Aldrete postanesthetic recovery score [21]
Intermediate	From PACU to discharge from hospital	Days	Self-care (able to care for self at home)	Symptoms and impairment in ADL	Quality of recovery score [22] Abdominal Surgery Impact Scale [23]
Late	From hospital discharge to return to usual function and activities	Weeks to months	Return to normal (baseline or population norms)	Function and health-related quality of life	Six-minute walk test [27] Community Health Activities Model Program for Seniors (CHAMPS) [25] Short Form-6D [26]

ADL activities of daily living, *OR* operating room, *PACU* postanesthesia care unit
Reprinted with permission from Lee et al. [4]

(SF-6D) [26]. The first of these, the 6-minute walk test, was originally developed to test exercise tolerance but is currently considered appropriate to test functional exercise capacity and accepted as a single measurement of functional status [27]. The CHAMPS instrument is a 41-item questionnaire developed to evaluate the effectiveness of interventions aimed at increasing the level of physical activity in elderly adults. Patients generally report the frequency and total time spent performing a range of physical and social activities during the prior week. This is then weighted according to the metabolic value of each activity, and thus a total caloric expenditure per kilogram per week is calculated [25]. The SF-6D is an indirect utility instrument used to measure effectiveness using quality-adjusted life years [26]. Once again, it is very important to understand that these tools are a few among many options in evaluating functional and physiologic recovery of the patient. One must always consider that the most crucial element of selection of a particular tool is the specific context of recovery in the unique time of interest.

Symptom Burden

A key element in the recovery of patients after surgery is the ability of the patient to return to full functional capacity and emotional well-being. In addition, patients and surgeons alike are concerned with either new or residual disability after surgery. The World Health Organization (WHO) International Classification of Functioning, Disability and Health classifies disability as "difficulties in any area of functioning as they relate to environmental and personal factors" [28]. Previous studies have shown that instruments measuring postoperative disability should focus not on symptoms but rather on the impact of such symptoms on psychological well-being, social involvement, life role activities, and cognitive well-being [29]. The MD Anderson Symptom Inventory (MDASI) is a versatile tool that has been found to be useful in demonstrating both symptom burden and functional interference (physical and emotional) secondary to symptom burden for cancer patients both in the immediate postsurgical period and after hospital discharge [30–32]. The MDASI is validated in multiple languages and has disease-specific modules for many areas such as spine, head and neck, lung, and ovarian cancer. The MDASI symptom interference score was found to be a good indicator of functional recovery after lung surgery as well as gynecologic surgery [32, 33]. Using a time-to-recovery analysis, gynecologic oncology patients who were treated on an ERAS pathway demonstrated a return to low or no total interference score (composite endpoint of interference from symptoms with general activity, mood, work [including work around the house], relations with other people, walking, and enjoyment of life) significantly faster than those not on an ERAS pathway. Such analyses can help measure functional recovery [32].

A recent study by Shulman and colleagues [34] aimed to evaluate the WHO Disability Assessment Schedule 2.0 (WHODAS) in a diverse surgical cohort with varying degrees of comorbid medical disease, disability, and health. A secondary aim of that study was to characterize disability-free survival after surgery. The WHODAS is a tool that measures disability, and it asks about limitations over the last 30 days in six major life domains: cognition, mobility, self-care, interpersonal relationships, work and household roles, and participation in society [35]. In that study, the authors evaluated 510 surgical patients and assessed clinical acceptability, validity, reliability, and responsiveness up to 12 months after surgery. The authors concluded that disability-free survival is an ideal study endpoint as it reflects the primary goal for most patients undergoing major surgery and can aid shared decision-making in surgical care.

One of the main challenges faced today when considering evaluation of ERAS programs on post-discharge recovery is choosing how we measure outcomes in a patient-centered fashion. One guiding principle to help guide what instruments to choose is thinking a priori why you are collecting the data.

For example, the instrument you choose to inform clinical care at an individual level might differ from an instrument one would choose for aggregate group comparisons (programmatic assessment). Additionally, consideration of recall period, timing of administration, and the sensitivity of the instrument for what one is trying to capture within surgical recovery must occur. Implementing PROs for supporting individual management requires thoughtful application of how PRO information is delivered back to the patient, caregiver, or clinical team so that it is easy to understand with guidance for action. For example, patients rating a severe range for lack of appetite might trigger an alert that leads to contact with a dietician, and those with severe fatigue for evaluation by physical or occupational therapists, while a high shortness of breath or pain score might alert the medical team to guide the patient to a more nuanced evaluation.

There is currently no perfect validated tool that is applicable to all patient populations, time points, or settings. In other words, specific instruments of outcomes measures may be valid only for unique conditions, thus leading to a broad range of measures and a lack of comparability between studies. However, there are likely enough similarities in certain aspects of functional recovery that we can strive to use common instruments.

The complexity involved with measurement of functional recovery also provides ample opportunity for future research and work. Instead of creating many new measures, can we agree on certain common measures? [36] To do so in an informed and patient-centered way, more work has to be done. Evaluating content validity, construct validity, reliability, and responsiveness of existing measures in various clinical scenarios is needed. With sufficient data, crosswalk algorithms can help us measure and compare across instruments.

Understanding the interpretation of PRO results is also important. The value of PRO measures depends on the extent to which stakeholders can interpret and potentially act upon the scores. Many results from PRO instruments are best thought about in a nonlinear fashion. More methodology work needs to be performed to identify scale categories that group results into mild, moderate, and severe symptoms/interference, as well as to understand clinically meaningful cut points. Partnering with experts in the field of patient-reported outcomes can help define minimally important differences and clinically meaningful differences that are more patient-centered outcomes for interpretation of functional recovery after surgery than the traditional statistical significance that we so often lean on [37].

Wearable Technology

Additionally, how will measurement of recovery change as we embrace the digital world? Computer-adapted testing can help decrease patient burden and improve precision [36, 38]. New technologies such as wearables are an inexpensive and easy way to get primary data regarding heart rate, sleep, movement, walking (steps), and location/distance via GPS tracking. Will data collection from wearables replace the old standards such as the 6-minute walk test? Data from wearable technology may complement or replace questions in PRO instruments that focus on sleep, walking, or activity. However, more work needs to be done to understand how to meaningfully interpret this data in reference to surgical recovery.

Conclusion

In conclusion, functional recovery after surgery occurs mostly outside the hospital environment. Two main challenges remain: (1) how to improve functional recovery after surgery and (2) how to measure functional recovery after surgery in a patient-centered manner. Post-discharge support of the surgical patient remains an area where we have an opportunity to improve ERAS programs. Harnessing digital technology and multimedia may provide novel and efficient ways to provide prompts for self-care (ambulation, diet) and provide severity-tailored feedback for self-management at home or guidance on when to reach out to the clinical team. Moving forward, more work is needed to improve our ability to measure and understand functional recovery after surgery and to meaningfully map responses to guide self-management or clinicians with management algorithms. In the meantime, when considering recovery instruments to measure outcomes, selection could be guided by what outcomes are most relevant to all stakeholders involved in the recovery of the patient while minimizing patient response burden.

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Recovery Within the Cancer Journey

31

Eve Simoneau and Thomas A. Aloia

Introduction

Perioperative medicine is an evolving and innovative field in the era of enhanced recovery pathways, since they were first applied in colorectal surgery almost three decades ago [1]. In order to improve patient safety and outcomes, perioperative components such as nonnarcotic analgesia strategies, surgical approaches, and postoperative care are continuously improving and aiming to provide optimal outcomes. Additionally, novel tools to measure patients' outcomes have also been introduced, such as patient-reported outcomes (PROs). Given the significant proportion of patients undergoing elective surgery for malignancy, the impact of an effective perioperative management strategy on oncological outcomes has also been evaluated.

Recently, a concept of timely return to intended oncologic treatment (RIOT) has been introduced [2], which represents a novel quality metric that cancer surgeons and physicians can use to evaluate the degree to which various perioperative interventions impact functional recovery in cancer patients. In this review, the data associating enhanced recovery, avoidance of postoperative complications, early return to adjuvant treatment, and favorable oncological outcomes will be explored, for several types of cancers, including hepatobiliary, and other malignancies.

The RIOT Concept

Long-term oncological outcomes, such as survival and recurrence, and generic short-term outcomes, such as 90-day morbidity and mortality, are known metrics after surgery. However, data reporting short- to mid-term outcomes that are relevant to cancer patients, such as pain relief, quality of life, functional recovery, and autonomy, are lacking. This deficiency in the literature prompted investigators to evaluate cancer-specific outcomes and to first define a relevant metric of recovery after surgery in cancer patients, defined as the time for return to intended oncologic treatment (RIOT). The RIOT concept has subsequently been used as a quality indicator for optimal oncological treatment sequencing, given the multimodal nature of most cancer treatments.

RIOT is characterized by two components: first, whether the patient did or did not return to intended oncological therapy after surgery, which constitutes a binary outcome, and, second, the time elapsed between surgery and the initiation of postoperative adjuvant therapies. Of course, the definition and measurement tools can be expanded to include capture of the complexity of the multimodal therapies for certain malignancies. As such, RIOT was additionally defined to quantify the extent of completion of the intended treatment pathway, to include not only completion of adjuvant systemic therapy – as an example – but the completion of other potential planned treatments, such as second-stage resection, interventional radiology procedures, endoscopic cancer therapies, radiotherapy, biologic and hormonal therapies, etc., in order to accurately measure the impact of postoperative recovery on the entire cancer treatment plan.

Prior to defining the RIOT concept, a few adjuvant systemic therapy trials were indirectly reporting the timing or completion of postoperative therapy, with no specific focus of RIOT as a quality indicator for oncological surgery. The initial study exploring the RIOT concept was comprised of patients who underwent liver resection for colorectal liver metastasis and reported a RIOT rate of 75%, with a median time to RIOT of 42 days [2]. Despite the paucity of data in the literature to benchmark against these results, we aimed to remodel our perioperative processes in order to improve these numbers. With the implementation of more optimal perioperative strategies within the framework of enhanced recovery, improved collabora-

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tions between the different providers, and refined patient coordination and scheduling, the RIOT rate was increased to 86% with median time of 36 days (unpublished data). Implicit in this calculus is that we believe that adjuvant therapy engenders a survival benefit to postoperative cancer patients. If this is accepted, then any impediment to postoperative recovery that prevents or delays RIOT will have a material impact on long-term cancer outcomes for the population of treated patients. This example supports the concept of RIOT as an objective quality indicator to gauge the effectiveness of oncology treatment pathways and hopefully to stimulate the implementation of superior system-based perioperative strategies within healthcare institutions that care for cancer patients.

RIOT was developed simultaneously as enhanced recovery in liver surgery (ERILS) pathways were being increasingly implemented. In the initial study, RIOT was assessed along with other standard dependent variables within the ERILS framework, and the authors were then able to determine that the enhanced recovery program increased the RIOT rate to 95% [3]. These impressive results further validated that the implementation of structured enhanced recovery programs not only standardize and homogenize perioperative care but that the effect of such program is extended beyond the immediate postoperative period. Further, it confirmed that independent of the technical aspects of the operation, the conduct of cancer patient care during the few days of the perioperative experience could have direct oncological benefits. Such results endorse the concept that enhanced recovery, although comprised of several individual elements that have shorter-term results, represents a system-based approach, which has long-term benefits for patients. Hence the effects of enhanced recovery programs cascade into better long-term outcomes, including better cancer-specific outcomes (Fig. 31.1).

Clearly, there is a direct mechanistic benefit of enhanced recovery pathways in avoiding postoperative complications that otherwise routinely obstruct initiation of postoperative cancer therapies. In addition, and likely to be further elucidated in the near future, there is emerging evidence that such a multimodal strategy has a positive effect in reducing perioperative stress response, thereby also potentially having a direct oncological benefit by modulating pro-inflammatory and immunosuppressive mediators.

Impact of Postoperative Complications and Riot on Oncological Outcomes

Hepatobiliary Oncology

For pancreatic ductal adenocarcinoma (PDAC), the overall 5-year survival remains low at 7% [4], and even the resected patients, who constitute the minority of all PDAC, obtain a 5-year survival of approximately 20% [5–8]. These results have only marginally improved despite reduction in postoperative mortality and advances in perioperative therapies [9]. The administration of adjuvant therapy for all tumor stages is a well-established fact for PDAC, as supported by data from randomized controlled trials such as ESPAC-1 and ESPAC-3, as well as the CONKO-001 [10–13]. However, due to the nature of the surgeries for pancreatic cancer and their associated morbidities, several studies investigated the relation between postoperative complications and delivery of adjuvant therapy, hypothesizing that the occurrence of complications could ultimately lead to delays or inability to receive adjuvant treatment, resulting in subsequently adverse oncological outcomes [14, 15]. Using a similar rationale and to improve patient selection and stratification, several institutions have also reported on the benefits of neoadjuvant therapy for resectable and borderline PDAC [16–19].

Regarding delays in postoperative therapy administration and outcomes, Wu et al. reported in a series of 1144 patients that patients with complications were more likely to have a significantly delayed return to therapy and subsequently worse OS (22.5 months vs. 10.7 months, respectively for patients who did not vs. did experience complications; $p < 0.001$) [14]. Interestingly, that detrimental OS difference was rescued if patients who experienced complications did not have delayed RIOT: patients who received adjuvant therapy after pancreaticoduodenectomy after a postoperative complication exhibited similar survival than patients who had an uneventful perioperative course (20.4 months vs. 22.5 months, respectively; $p > 0.05$). Lastly, patients who did not undergo adjuvant therapy had worse survival, independent of having a complication.

Several studies that used data from national databases such as the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) and the National Cancer Database (NCDB) indicated that a rela-

Fig. 31.1 A working paradigm describing the influence of enhanced and standardized perioperative care on oncologic outcomes after cancer surgery

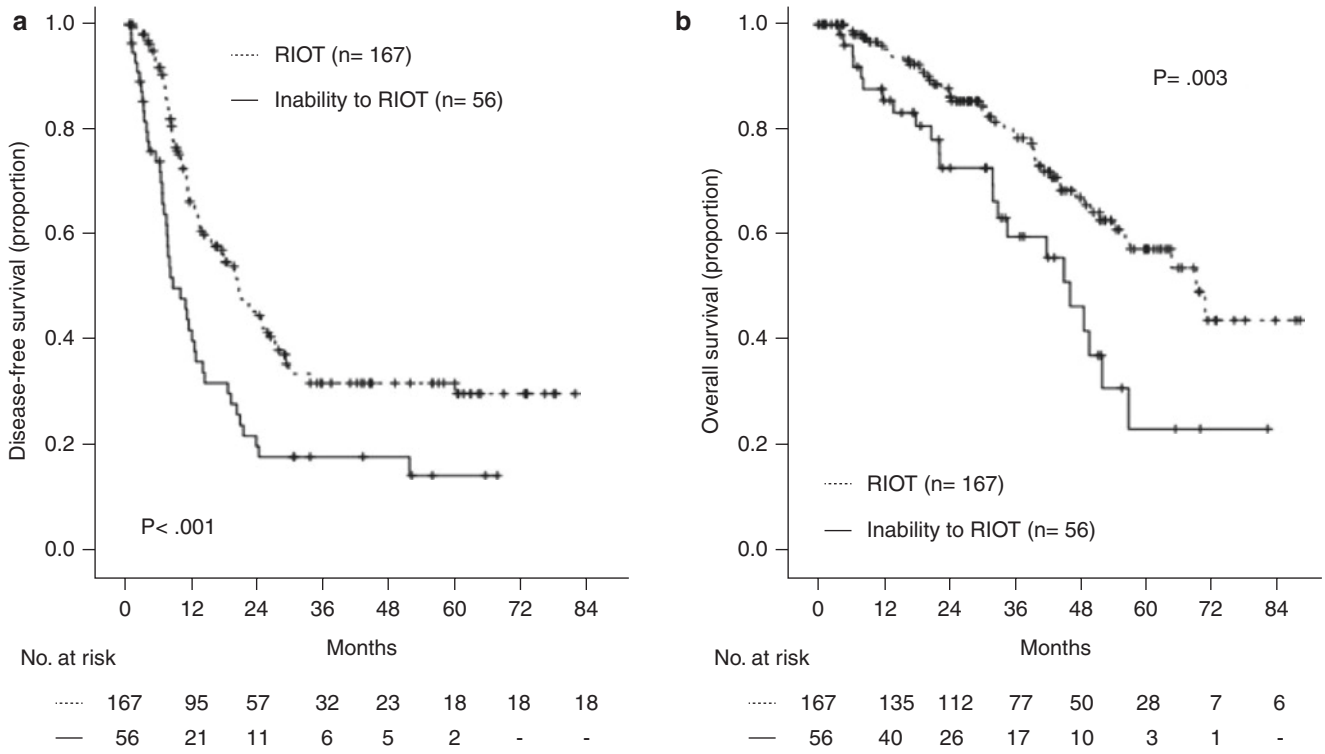

Fig. 31.2 Recurrence-free and overall survival for patients undergoing open hepatectomy for colorectal liver metastasis (n = 223), stratified by RIOT and inability to RIOT. RIOT, return to intended oncologic treatment. (Reprinted with permission from Aloia et al. [2])

tively high proportion of PDAC patients – over 30% – will never receive postoperative therapy [15, 20, 21]. In fact, Merkow et al. showed that 61.8% of patients who did not experience a complication following pancreatic resection for stages I–III pancreatic adenocarcinoma had receipt of adjuvant chemotherapy, while only 43.6% patients who suffered from a serious complication after pancreatic resection had receipt of adjuvant chemotherapy. In addition to reporting a clear correlation between complications and RIOT (OR = 2.08, 95% CI: 1.42–3.05), the same study revealed a median RIOT of 70 vs. 52 days for patients experiencing postoperative complications vs. no complications [15]. In the enhanced recovery literature, favorable outcomes have been reported for pancreatic cancer surgery, including short-term outcomes such as DGE reduction in the enhanced recovery program arms [22]. Overall, the implementation of clinical pathways for PDAC has been shown to have significantly positive impact on hospital cost and length of stay, without negative effects on postoperative adverse events and complications [23], although the direct impact of clinical pathways on RIOT remains to be investigated.

Regarding liver resection, the benefits of implementing ERILS pathways were also evident given that ERILS promotes a multimodal approach that aims to reduce complications, in addition to be associated with less perioperative inflammation, decreased transfusions, reduced opioid requirements, and overall efficient recovery. Analyses [24, 25] have demonstrated clear evidence that postoperative complications have a negative oncological impact in patients undergoing resection of colorectal liver metastasis (CRLM), in terms of worse disease-free survival and overall survival. Postoperative complications can preclude timely RIOT, as it was shown in the first validation study published by Aloia et al. where patients with CRLM with delayed or omitted timely adjuvant therapy were more likely to have experienced postoperative complications (p = 0.039) [2]. As expected, this non-RIOT group exhibited significantly worse disease-free and overall survival (Fig. 31.2). These findings were corroborated in a study where ERLS patients had significantly superior survival after 2 years compared to traditional pathway, implying an advantage of this strategy that extends beyond the immediate postoperative period [26]. Further studies should aim to evaluate the exact interactions between ERILS, inflammation, and RIOT.

Breast Cancer

It is now proven that completion of adjuvant breast cancer chemotherapy has a significant effect on OS. Moreover, the amount of adjuvant chemotherapy completed is an important factor associated with OS, which was demonstrated in previ-

ous randomized controlled trials [27, 28]. In fact, Nurgalieva et al. found that survival was significantly impaired when patients received adjuvant chemotherapy beyond 3 months after surgery. RIOT and optimal functional recovery are also important in patients who receive neoadjuvant chemotherapy or who do not require chemotherapy and will receive radiotherapy as their next treatment regimen after surgery. Patient must have recovered from their surgical procedure and any complications and have full range of motion of their arm for proper positioning during radiation. Several studies show the impact of delays to radiotherapy on local recurrence rates, even in early-stage patients, which translates into higher risk of locoregional recurrence when therapy is delayed to more than 8 weeks postop [29, 30]. Although these data do not specifically discuss enhanced recovery or postoperative complications directly, these studies still provide the most compelling argument that the various components of RIOT should be measured in breast surgery patients and likely have a direct impact on cancer outcomes. Perioperative strategies, even in breast surgery where morbidity can be relatively lower compared to procedures for other malignancies, should focus on rapid and complete patient recovery for optimal long-term outcomes.

Conclusion

This chapter summarized data indicating that a multicomponent, standardized, and evidence-based approach to perioperative care has the potential to impact cancer-specific outcomes. The advantages of enhanced recovery pathways are particularly relevant for patients with malignancies, as they often have longitudinal treatment strategies that are absolutely dependent on optimal functional recovery to achieve optimal long-term oncological outcomes. For these patients, the benefits of enhanced recovery certainly extend beyond the commonly reported short-term outcomes such as length of stay, morbidity, mortality, and costs. Given these positive attributes, ongoing efforts are required to facilitate wider implementation of such programs in the surgical community. Ultimately, as all cancer treatments cause some degree of patient disability, the patients' best interests can only be addressed by oncologic providers who are accountable to continuously strive to understand and improve mechanisms of recovery.

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Readmission Challenges and Impacts Within ERAS

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Introduction

Among the primary goals of any enhanced recovery after surgery (ERAS) protocol is to decrease the amount of time patients remain in the hospital after surgery. While decreasing length of stay (LOS) is a critical part of that initiative, it remains only half the battle. Rushing patients to discharge, only to have them come back in increasing numbers, would do nothing to help them or to advance the principles of ERAS. This chapter will focus on readmissions within ERAS and how we may be able to improve in this particular aspect.

The Burden of Postoperative Readmissions

Research into the medical, financial, and emotional burdens of postoperative readmissions on patients, surgeons, and hospitals [1, 2] only scratches the surface of a particularly frustrating topic. Being cleared for discharge and then returning with unresolved complaints can be an upsetting experience for patients and may even erode patient trust in the judgment of the discharging physician. A 2015 American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) review of postoperative readmissions looked at 498875 operations, including bariatric procedures, colectomy, proctectomy, hysterectomy, total hip or knee arthroplasty, ventral hernia repair, and lower extremity vascular bypass [3]. It demonstrated a 30-day readmission rate of 5.7%. The most common reason for readmission was surgical site infection (19.5%) [3]. A subsequent evaluation of the Nationwide Readmissions Database demonstrated that of nearly 60,000 patients undergoing complex oncologic resection (defined as esophagectomy, gastrectomy, hepatectomy, pancreatectomy, colorectal resection, lung resection, or cystectomy), 14% were readmitted within 30 days of operation, 82% of these readmissions were deemed potentially preventable [4].

The Affordable Care Act, established in 2010 in the United States, introduced the Hospital Readmission Reduction Program (HRRP). This initiative tightened financial penalties on hospitals with higher than expected 30-day readmission rates [5]. Beginning in 2012, hospitals began to see the impact of these penalties, as a forfeited percentage of their total Medicare reimbursement. There is data to suggest that the HRRP has succeeded in yielding decreased readmission rates [6], while there is evidence that the initiative actually resulted in longer index hospital stays [7]. This political environment places even more pressure on US ERAS centers to avoid any increase in readmissions despite decreasing length of stay.

Discharge and Readmission in the ERAS Era

There is a wealth of literature supporting the idea that employing and adhering to ERAS principles lead to significant decreases in length of stay; however, it could be argued that by striving to comply with ERAS metrics, physicians may be prematurely discharging patients, potentially setting the stage for an increased number of readmissions. So do ERAS protocols lead to increased readmission rates? Fortunately we do

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not have to rely on speculation, as a number of recent studies have evaluated the impact of ERAS on readmission rates. The following section will present selected high-quality studies and consider their impact on this discussion. The presented papers are divided into two sections: those that did not demonstrate a significant increase in readmission rates among ERAS patients and those that did.

Studies that Showed Similar Readmission Rates Between ERAS and Conventional Recovery Groups

Colorectal Surgery

In a 2017 study, all patients undergoing elective colorectal surgery at 15 academic hospitals in Canada (n = 2876) were enrolled into ERAS protocols and followed prospectively for 30 days. The objective was to review ER visits and readmission rates as well as reasons for both. The study revealed a shortened length of stay, which was not associated with increased rates of readmission [8].

A 2017 retrospective study involving 20 centers in Northern California compared outcomes before and after ERAS implementation in two populations: elective colorectal surgery (n = 3768) and emergency hip fracture repair (n = 5002). The ERAS pathways in that study were introduced in 2014. This study clearly demonstrated a decrease in length of stay in both groups (5.1–4.2 days in the colorectal group and 3.6–3.2 days in the hip fracture group), with no change in readmission rates [9]. Importantly, coordination of ERAS introduction to these centers was facilitated with the aid of a regional ERAS summit, including more than 400 staff members. Standardized electronic order sets were also incorporated to ensure standardized practice.

A 2018 retrospective review across 15 Canadian institutions included 2876 patients undergoing elective colorectal surgery. This study demonstrated that ERAS compliance was linked to "optimal recovery" in a multivariate analysis. A necessary component of "optimal recovery" was "no readmissions." The benefit of ERAS compliance was more pronounced in open procedures but significant in minimally invasive procedures as well. The overall readmission rate was <8% [10].

Another 2018 retrospective review analyzed the postoperative outcomes of 2714 patients who underwent colorectal surgery in Alberta, Canada. These patients were divided between two groups depending on whether they were recovered before or after ERAS implementation [11]. This study found no difference in readmission rates between the two groups.

Non-colorectal Abdominal Surgery

A 2016 retrospective study enrolled 100 patients undergoing major ventral hernia repair with transversus abdominis release and mesh sublay into an ERAS recovery pathway [12]. Outcomes were compared to a historical cohort from before institution of the ERAS protocol. Average length of stay in the ERAS group was 4 days, reduced from 6.1 in the pre-ERAS cohort. Strikingly, 90-day readmission rates for the ERAS group actually decreased to 4%, from a historical rate of 16% [12].

A 2017 prospective study randomized 159 patients undergoing Whipple procedure in China into either ERAS pathway or conventional recovery [13]. The ERAS group demonstrated significant decrease in time to first bowel movement and in length of stay, with no impact on 30-day readmission rate [13].

A 2018 systematic review and meta-analysis included 39 studies (14 randomized and 25 cohort) comparing ERAS vs. conventional recovery in non-colorectal abdominal surgical procedures [14]. A total of 6511 patients were included in the analysis. The ERAS group had a significant decrease in length of stay (reduction of 2.5 days overall or 2.6 days when including only randomized studies), without an increase in readmission rate [14].

A 2018 meta-analysis of ERAS vs. non-ERAS protocols after pancreatic surgery included 3694 patients operated on from 1995 to 2017. This study showed no difference in 30-day readmission rates between the two groups [15].

Urology

A 2017 randomized pilot study in Vancouver compared ERAS to standard recovery after radical cystectomy and urinary diversion. The ERAS group had significantly shorter length of stay and time to return of bowel function without significant difference in readmission rates [16].

A 2018 retrospective single institution study at Johns Hopkins compared 56 consecutive ERAS patients to 54 pre-ERAS patients after radical cystectomy. The ERAS group had significantly decreased length of stay with no significant difference in readmission rates [17].

Transplant

A 2018 retrospective study at the University of Buffalo evaluated 1 year of consecutive kidney transplants after ERAS protocol (n = 139) and compared outcomes to a historical pre-ERAS cohort. This study showed decreased length of stay with no difference in readmission rates [18].

Thoracic Surgery

A 2018 retrospective evaluation of outcomes after lung resection at MD Anderson divided patients into three groups: pre-ERAS (2006–2011), in transition (2011–2015), and post-ERAS (2015–2017). A total of 2886 patients were included in the study, which demonstrated decreased length of stay with no impact on readmission rates [19].

Gynecologic Oncology

A 2018 study incorporating 152 pre-ERAS and 367 post-ERAS looked at patients undergoing debulking of gynecologic malignancy at Alberta Health Services hospitals. Median length of stay for all surgeries was significantly decreased, and there was no significant difference in readmission rates [20].

Studies that Showed an Increased Readmission Rate After ERAS Recovery

A 2017 systematic review and meta-analysis of only randomized comparisons between ERAS and non-ERAS protocols (8 studies with 801 patients from 1994 to 2016) after gastrectomy showed decreased length of stay in the ERAS group but significantly increased readmission rates (odd ratio 3.42) [21].

Another 2018 meta-analysis of only randomized comparisons between ERAS and non-ERAS protocols, including 1092 patients after gastric surgery, showed significantly increased readmission rates in ERAS group [22].

Institutional ERAS Readmission Data

At Carolinas Medical Center, a US-based ERAS® Center of Excellence, ERAS pathways have been initiated for pancreaticoduodenectomy, left pancreatectomy, and liver resection [23]. At the time of analysis, these groups included 153, 73, and 98 patients, respectively. Clinical data, including ERAS compliance, has been prospectively collected via the ERAS® Interactive Audit System (EIAS). Since initiation of ERAS, 30-day readmission rates have fallen from 25.0%, 25.5%, and 17.0% to 23.5%, 24.7%, and 11.2%, respectively (Table 32.1). It is important to note that ERAS must be enacted in its entirety with a dedicated, multidisciplinary team enforcing compliance. Implementing enhanced recovery protocols, without the organizational framework of formal ERAS, has been shown to lead to a gradual but significant compliance drift [24]. The importance of high compliance cannot be overstressed, as compliance has been tied to improved outcomes [10, 25].

Table 32.1 Readmission rates (30-day) at Carolinas Medical Center, 1 year from initiation of ERAS protocols by the Division of HPB Surgery

Implementation	Distal pancreatectomy	Liver resection	Whipple	Total
Pre-ERAS	25.5% *n* = 51	17.0% *n* = 53	25.0% *n* = 48	22.4% *n* = 152
ERAS	24.7% *n* = 73	11.2% *n* = 98	23.5% *n* = 153	20.1% *n* = 324

Postoperative Emergency Room Visits Not Requiring Readmission

With few exceptions, the available data seems to overwhelmingly suggest that adhering to an ERAS protocol does not significantly increase readmission rates. However, one potential consequence of ERAS that may not be captured by readmissions data is an increased rate of postoperative emergency room (ER) visits that do not lead to readmission. It would be reasonable to expect that abbreviated inpatient recovery and accelerated discharge would lead to patients being sent home at earlier stages of wound healing, with more dependence on pain medications and with less time to adjust to postoperative symptomatology without the benefit of constant access to their care providers. This might in turn lead to a higher incidence of concerned patients returning to the emergency room with minor complaints. Even without readmission, postoperative emergency visits can be inconvenient for patients and lead to increases in healthcare costs. A 2016 review of postoperative emergency room utilization among 38,776 bariatric operations in New York State demonstrated that nearly two-thirds of postoperative emergency room visits did not lead to readmission [26]. An evaluation of postoperative emergency room visits should be a mandatory inclusion in any discussion about ERAS readmission rates.

The most comprehensive evaluation of postoperative emergency room utilization in the ERAS era comes from a recent review of 2876 patients (across 15 academic institutions) who had undergone colorectal surgery followed by recovery under an ERAS protocol [8]. Decreased length of stay seen in these ERAS patients was not associated with an increase in readmission rates or an increase in emergency room utilization. Of the patients, 11.6% returned to the emergency room but were not readmitted, while 8.2% were readmitted. Wound complications were the most common reason for emergency room visits not requiring readmission (44.5%) [8]. While these data are encouraging in regard to the safety of accelerated discharge after ERAS recovery, they also clearly demonstrate the importance of including emergency room utilization in studies evaluating the post-discharge costs and consequences of ERAS. They also promise opportunity for improvement. The fact that the most common reason for emergency room utilization is patient wound concern indicates that we, as surgeons, should be directing focused initiatives toward both anticipating and preventing scenarios in which patients return to the ER for minor wound care problems. This will likely involve a multidisciplinary effort among surgeons, nurses, wound care specialists, and social workers, including formalized pre-discharge education, as well as post-discharge home care. There may also be a role for predictive analytics in determining which patients are at risk for return to emergency room with minor wound complaints. A 2017 study from the urology literature articulated

this concept by revealing that among 28,635 women undergoing outpatient urethral sling procedures, 81% of unplanned hospital visits within 30 days were emergency room visits not requiring readmission [27]. The study went on to conclude that standardized recovery room algorithms and postoperative patient counseling may be easy ways to reduce the unnecessary cost and inconvenience to patients.

Patient and Physician Perspectives

An evaluation of ERAS readmissions would also be incomplete without discussing the perspective of patients and physicians regarding comfort with early discharge and concerns over readmission. A survey sent to 496 patients who underwent elective colorectal surgery at an academic hospital from 2012 to 2015 revealed that 90% felt that they were ready for discharge and 88% were satisfied with the follow-up plan [28]. While these numbers were encouraging and on par with pre-ERAS estimates, a significant number of patients voiced concern over lack of postoperative discussions. Notably, some felt that they were not informed about common postoperative occurrences, including readmissions, or how to resolve anticipated complications [28]. A 2016 survey of physicians and patients demonstrated the importance of perceived barriers and facilitators inherent in introducing a standardized ERAS pathway to a real-life population [29, 30]. Some of the most raised issues included questions over adequate social support, early mobilization, need for additional patient education, effective pain control, and concern over unforeseen complications or readmissions. Interestingly most of these are related not to medical care but rather to improved communication and functional discharge planning.

Predicting and Preventing Readmission

Prediction of readmission has proven to be an elusive goal in both surgical and medical arenas. Numerous studies have been carried out with the aim of predicting which patients are likely to be readmitted after discharge, with mixed success. Some of the more reliable predictors include occurrence of postoperative complications and severity of preexisting comorbidities [31]. Attempts at more sophisticated risk assessments using biomarkers [32], nutritional lab values [33], and timing of interventional procedures [34] have provided less consistent results. Taken as a whole, existing studies have deciphered a complex web of independent predictors of postoperative readmission. Many of these are related to the patient's medical history, such as age, chronic obstructive pulmonary disease (COPD), depression, hypertension, diabetes, iron-deficiency anemia, and obesity [35]. Others, such as insurance status and type of insurance, are not [4], although this is not universally accepted. In another study, Medicaid patients had higher readmission rates than patients with private insurance [4]. On the other hand, a 2016 review evaluating risk factors for emergency room utilization after bariatric surgery found that among the five most significant risk factors for return to hospital, three had nothing to do with medical history or type of surgery performed (insurance through Medicaid/Medicare, patient race, and distance traveled from home for index operation) [26].

Each patient arrives at the discharge decision-making process accompanied by a huge number of preoperative, intraoperative, and postoperative variables. Attempting to distill that vast quantity of data into a simple yes or no decision regarding discharge may seem a nearly impossible task. In that setting it is understandably tempting to rely on a gut reaction from a seasoned physician rather than an evidence-based calculation. One ambitious target moving forward is to combine the emerging fields of predictive analytics, artificial intelligence, and precision clinical medicine to provide a new generation of easy-to-use, patient-specific risk calculators.

One promising new concept in predictive analytics is the incorporation of artificial intelligence and machine learning. Many targets of predictive analytics, such as length of stay and readmission rates, are nonlinear in nature. As a result, traditional linear regression modeling techniques have been notoriously poor at creating accurate predictive models. Machine learning techniques may offer a way around this problem. For example, kernel-based regularized least squares (KRLS), a machine-learning-based method, has demonstrated utility in protecting against the misspecification biases typically associated with traditional regression models [36]. KRLS is a nonlinear technique, which has already begun to establish a role in the medical literature as a means to construct more accurate predictive models, especially in regard to nonlinear parameters [37, 38]. Machine learning analytics has not yet been widely applied to predicting readmission rates but will likely play a key role if the surgical community endeavors toward evidence-based readmission risk calculators to inform discharge decisions.

How Can Modifiable Risk Factors That Can Be Addressed Preoperatively Lead to a Decrease of Readmission Rates?

Based on the existing data, it seems clear that adhering to an ERAS protocol does not increase readmission rates. While this is encouraging, it should not lead to complacency. In other words, we should not settle for equivalence when we may be able to do even better. One fundamental goal of ERAS has been modification of preoperative factors

with the aim of improving postoperative outcomes. An exciting potential avenue of advancement is the refinement of preoperative optimization to drive readmission rates down even further.

Multimodal Prehabilitation

Prehabilitation is a topic that has recently garnered attention across multiple surgical disciplines. A 2018 systematic review and meta-analysis of randomized and cohort studies compared the employment versus omission of nutritional prehabilitation before elective colorectal surgery. Prehabilitation led to decreased LOS and accelerated functional recovery [39]. Nutritional optimization, however, is only scratching the surface of prehabilitation potential. As currently described, there are five key pillars of prehabilitation as practiced at our institution: optimized diet, prescribed exercise, smoking cessation, hyperglycemia/anemia correction, and psychological support/teaching. While there is abundant data supporting the benefits of each of these pillars in isolation, there have been no high-quality studies quantifying the comparative benefits of a comprehensive prehabilitation program with respect to postoperative outcomes and readmission rates. A recent systematic review, incorporating 2591 patients, explored the effects of prehabilitation programs on outcomes after major abdominal surgery [40]. The study concluded that there is likely benefit to multimodal programs; however, existing protocols are too heterogeneous to allow for meaningful statistical analysis. There is a definite need for continued analysis as prehabilitation studies become more standardized. It will also be interesting to see how they complement existing ERAS measures.

One example of adding a technologic twist on the idea of prehabilitation is adding the use of digital fitness tracker being explored at Carolinas Medical Center. A 2018 pilot study enrolled 22 patients with planned pancreaticoduodenectomy, who were assigned digital fitness tracker devices at the time of preoperative education class with instructions to continue wearing the device through postoperative day 60 [41]. ERAS nurses tracked daily activity levels (which were stratified into five groups based on daily step counts: inactive, sedentary, semi-active, active, and very active). Patients were contacted whenever activity levels decreased. This study, even in the pilot stages, showed a clear link between increased activity and decreased length of stay coupled with a decrease in readmission rates.

Focused Preoperative Patient Education

Our institution utilizes a standardized preoperative education class for all patients intended to recover under an ERAS protocol. The education activity is attended by patients after their preadmission screening appointment. This 60-minute class is led by an ERAS nurse and supplemented by educational materials, including an interactive, educational notebook. The effectiveness of these classes has been demonstrated by comparisons between pretest and posttest scores evaluating a patient's understanding of the intended procedure and expected postoperative course. Classes have also helped to foster a sense of community and lasting relationships between patients undergoing similar operations, as well as their family members [42]. There are currently no standardized postoperative educational programs described in the literature, but this would certainly be an intriguing area of development moving forward, as they would be able to focus less on the technical nature of the procedure and the first days of recovery and more on common post-discharge issues, such as wound complications.

Conclusion

Early discharge after surgery is not in itself an ERAS compliance measure. The decision to discharge a patient from the hospital should remain in all cases the endpoint of a nuanced and highly personalized algorithm, often extending beyond a patient's clinical picture. Declaring a patient safe for discharge depends upon a myriad of patient-specific factors, many of which necessitate wide deviations from the length of stay anticipated for a given operation. Some of these include baseline pain tolerance and previous opioid exposure, capacity and willingness to carry out dressing changes and drain maintenance, availability of family and social support, baseline mobility, and history of compliance with physician recommendations. A patient with a long operative history may be much more comfortable with complex wound care at home than one who has never before had an incision. The availability of visiting nurse services and more expensive medications are often dependent on a patient's health insurance coverage. Baseline anxiety may lead a patient to return for more frequent postoperative emergency room visits. In short, no patient population is truly standardized and at no time is this more evident than when transitioning patients to an environment that is beyond the control of their healthcare providers.

A preconceived notion exists that since ERAS protocols lead to accelerated discharge, they may also lead to increased readmission rates. The data, however, do not support this suspicion. ERAS protocols have consistently led to decreased length of stay, without a measurable impact on readmission rates or emergency room utilization. The focus now should be on decreasing readmission rates even further within the context of ERAS protocols by anticipating and preventing readmissions with the aid of preoperative optimization (multimodal prehabilitation), improved communication and patient teaching, and perioperative predictive analytics.

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An Example of a Patient's Experience in ERAS

33

Garry Laxdal

This chapter is about hope and belief! When I was diagnosed with rectal cancer in June of 2015, I had never even heard of an abdominoperineal resection (APR), let alone what enhanced recovery after surgery (ERAS) was. When you are a healthy 53-year-old and told you have Cancer, you often do not think of anything else. It is really hard to think beyond the "C" word, as you feel the world is crashing down around you. Up until that moment, my interaction with the healthcare system had been very minimal. Recently retired from owning a technology company, I was averaging just over 100 rounds of golf throughout the year, was an avid hunter in the fall, and did house renovations in my spare time.

What I did know is that I had a disease that involved extensive treatment followed by major surgery. Right from the outset of my diagnosis, I knew I had to take an active participation in my cancer journey, if there was to be a successful outcome.

As ironic or as corny as it sounds, I had confidence the medical team that I was introduced to were the experts in their fields, highly trained to treat patients with cancer. They had multiple years of education followed by years of practice to become leaders in their field of healthcare. What I felt I needed to do, on my part, was to put myself in the best physical, mental, and spiritual shape going into my surgery and treatment. My reasoning was to better my odds of a successful recovery afterward. Again, ERAS was not even front and center in my mind…yet. As you will see, I am a very goal-oriented person, and I enjoy challenging myself with keeping busy with projects and tasks.

The great part about working with the healthcare professionals at Alberta Health Services (AHS) is that you are made to feel like you are an active participant in your care and a part of the medical team. I was to have 2 months of radiation and chemotherapy treatment followed by a short break and then surgery. ERAS was first introduced to me during one of my appointments with my surgical team in the form of informational pamphlets. At first there is an overwhelming overload of things to do and of information to process in the form of appointments, treatments, and understanding services and also dealing with the family and psychological aspects of having cancer. As I mentioned earlier, it is hard to hear to anything past the "C" word, and I did not know what to do with the information handouts on ERAS that were given to me.

What I did find helpful was the patience (pun intended) that was shown to me by my medical team in explaining what ERAS was…multiple times. I think the secret to having ERAS rolled out effectively is to introduce it and discuss the concepts and program multiple times with patients. At first, we patients do not hear or, most likely, cannot listen to the information when it is provided to us. When I did finally figure it out, it was like a light switch that was turned on, and I truly had an "Ah Ha Moment." The healthcare money savings that I later heard about are very real and evident with ERAS, but that was not my motivator. Getting out of the hospital as quickly as possible after surgery was my prime motivator. Faced with a length of stay in the hospital post-surgery anywhere in between 7 and 21 days was not going to fit with my desire nor my lifestyle, and I had to shorten this up considerably. Being alive and able to golf 3 months post-surgery was my goal and motivator.

All my life, I have been taught to never do a job halfway but to give 100% of my energy and focus. It then became my mission and job to learn as much about my treatment, surgery, and enhanced recovery after surgery as possible. The literature available to me on ERAS was good, but I became an information junky trying to learn as much about my surgery and ERAS as possible, to safeguard my future. By scouring the Internet, studying all of the recommended readings provided by AHS and also the resources available from a nonprofit Canadian organization called Wellspring, bit by bit I was learning and gaining an understanding of rectal cancer and the benefits of ERAS. Websites such as

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www.errassociety.org, www.patientsafetyinstitute.ca, and www.albertahealthservices.ca were also very informative. Whether it be pamphlets, online readings, surgery learning modules, or other educational resources, all of the information was welcomed and extremely comforting. ERAS gave me hope—true hope in the form of me having some direct impact on my care and something to look forward to and to focus on. My job was to do everything possible to get ready for not only my surgery but the long recovery road afterward. My goal was simple, to focus on following the ERAS guidelines and to get my body ready for major bowel surgery. Putting my energy and attention into ERAS practices allowed me to think and worry just a little bit less about my cancer and upcoming surgery. The mind often goes to "dark places" when you have cancer, and ERAS was certainly a tool I used to divert this way of thinking.

I did not know at the time, but I was already well on my way to doing my part for ERAS, and unknowingly I was preparing for surgery and the recovery afterward. Walking 3–5 km/day with my dog was the norm for me, as well as golfing almost every day that summer helped me to be in good physical condition. My mindset told me the more I worked on and improved on my fitness prior to surgery, then the better the outcome would be post-surgery.

My "Medical Team," which consisted of a radiation oncologist, medical oncologist, surgeon, family doctor, and myself, spoke frequently; and together we made decisions. I also set up my own "Personal Team," which consisted of my wife, daughters, a few very close friends, family members, and my dog. Constantly reaching out to both of my teams and discussing questions, issues, and fears also assisted me in preparation with ERAS and planning. Utilizing two unique and separate teams was a great benefit and allowed me to overcome many physical and mental challenges from my diagnosis.

Mindfulness was also introduced to me, to assist in my mental and spiritual coping with cancer. I would never have thought that I would meditate in my lifetime. Once I was informed that practicing mindfulness would have a statistically proven positive and dramatic effect on my recovery, I was propelled further into learning something new, and my wife and I enrolled in an outstanding course called Mindfulness-Based Cancer Recovery (MBCR), offered by our healthcare system (AHS).

The other ERAS guideline preparations done before surgery are cutting down on alcohol consumption, resting more, and switching to a higher carbohydrate diet about 2–3 weeks prior to my surgery and post-surgery taking pain medications recommended by my healthcare teams.

Just prior to surgery, I had a meeting with the Pre-Admission Clinic to go over the upcoming surgery treatment. At that time we also went over the ERAS guidelines pertaining to what to expect during my stay at the hospital and how following the post-surgery instructions were paramount to my well-being and successful recovery.

Before I knew it, the time had come for my surgery. All the preparations within my control were done following the ERAS guidelines, except to drink a big glass of apple juice 3 h before my surgery to boost my carbohydrates. After the fasting, the apple juice tasted great and was a great way to start the day of my surgery!

In the Hospital

The day of my surgery was actually a relief. I was no longer waiting for my surgery and prep work. After waking up from anesthesia in the post-anesthesia care unit (PACU), water, juice, and cookies were offered to me, which were gladly accepted. Once transferred to my room a few hours later, I felt good, and the pain was very manageable. My pain medications had included an epidural as well as an IV with Hydromorph. I found that I was quite thirsty and found relief by drinking many glasses of water. Good thing that I was given a catheter, which assisted immensely! Chewing gum also felt good, and I knew that it would help get my digestive system going again more quickly. The evening of my surgery, with assistance, I was able to get out of my bed and take a short walk. Even though I was a bit nauseous, it felt good to feel the weight of my body on my legs. While not part of my ERAS program, with a nod from nursing staff, I was brought in food the night of my surgery by my family, as I was very hungry and felt I could eat solid foods right away. There were no adverse effects from this and actually felt quite the opposite…it felt normal. An incentive spirometer was given to me to help strengthen my lungs and keep them clear. I took this as a challenge to get better and made it a goal to get better each day with this device. At first it was hard and exhausting to use, but gradually it got better day after day.

Day 1 after surgery was good. I was able to get up and walk the hospital ward corridors some four or five times that day. In addition to the food that the hospital provided for me, as well as what seemed an endless supply of nutrition drinks, my daughter brought me comfort food from home, which made me feel better. My pain in the days after my surgery was very minimal (pain level 2), and by the end of day 2 post-surgery, I requested to be taken off my epidural and IV pain medication as I found it was giving me a headache and was more painful than my APR surgery incisions. Each day I was able to walk more and more and was getting stronger continuously. My fluid intake also increased as well, and a full appetite was back. The nurses and doctors were pleased that I was augmenting the hospital diet with foods that family and friends were bringing me. From day 3 to day 5, I spent a lot of time learning how to take care of my stoma, exercising more by walking the corridors, doing leg exercises, and

blowing into the incentive spirometer. Everything that I had learned in my ERAS preparation and following the guidelines seemed to help considerably. It was almost unbelievable how good I was feeling. One hears of the many horror stories that some patients have recovering from surgery, and I was extremely happy that I had none of the poor outcome stories to share. My care by the medical team was fantastic and was proud of my accomplishments for being part of the ERAS treatment plan. Continuing my mindfulness practice by meditating helped me try to sleep better at night and assisted in my overall well-being.

Not all of my hospital stay after surgery was rainbows and unicorns so to speak. Rest, true rest, is almost impossible to get while you are in a semiprivate ward with a roommate. There is always a flurry of activity going on, and the noise level is quite high. Whether it was the lab people collecting blood, nursing staff checking in on me, housekeeping cleaning, or my loud roommates, my frustration levels due to a lack of rest and sleep were quite high. It seemed for a while that I would never be discharged quickly enough, and this was sometimes discouraging. I was fortunate enough to have my personal support team help me through these challenging times by discussing issues and helping me cope. My physical health was improving, but the mental health seemed to be catching up to me, and I was sometimes feeling quite drained.

After Discharge Experience

On day 5 after surgery, I was discharged and allowed to go home. Being discharged on day 5, when originally told I was going to be in the hospital anywhere from 7 to 21 days, was like winning a lottery! This was solid proof to me that all the ERAS preparation prior to and right after surgery worked.

When I walked into my home, I started to cry, and I was overcome with emotion. The feeling of being home again and to feel the soft touch of my sheets on my own bed was a blessing. I had learned in the Mindfulness-Based Cancer Recovery of a practice called Beginners Mind, where you look at everything as if it is the first time you see it and that everything is a miracle. This was exactly how I felt. After resting a good portion of the day, and after doing my exercises, I was almost giddy in how everything was brilliant and wonderful. My wife took me on an assisted walk around our neighborhood block, and I felt no pain or nausea. What a relief! That evening we had a marvelous home-cooked meal, and I had no problem sleeping. Words cannot express how I felt that night sleeping in my own bed in silence surrounded by love and comfort. Hospitals are a nice place to visit, but there's no place like home.

The days to follow consisted of taking progressively longer walks with my dog and getting back to my routine (as normal as possible). I did follow the doctors' orders and did not lift anything heavier than a jug of milk and stopped doing any activity if I felt I was overdoing it. It is funny how your body will let you know if you are doing too much activity; you just need to listen. Pain medication was prescribed to me and was only used sparingly at best as I felt good.

I should note that I have always had a fear about overmedicating with pain meds. While going through my radiation and chemotherapy treatments, I experienced a considerable amount of pain. The pain seemed worse, and I felt that the pain meds were not working. One of my personal support team members is a physician, and I remember him saying how important it was to stay ahead of the pain. When I expressed to him how I feared becoming addicted to the pain meds, his reply was simply to listen to your body and stay ahead of the pain to help with not only my physical pain but also my mental well-being. Was I under medicating? I'm not sure, but I found by talking about it with others as well as practicing mindfulness greatly helped.

The only negative interaction I had was to take a daily injection of blood thinners to prevent blood clots. This was a small price to pay in the big scheme of my recovery. Each day, I was getting stronger and stronger. Shortly thereafter I was making and eating regular meals and could walk further and further each day. My continuation of mindfulness meditation and yoga nidra also was a great way to relax and focus on getting better and stronger. When I had moments of doubt about my future with an ostomy, I would use the meditation and my personal team to help get me through the dark hours. Within 3 days of being home, I was able to stop using the incentive spirometer as I was consistently producing a strong breath and my lungs felt great.

As Christmas season was coming upon us, I was able to begin making holiday preparations around the house and also continue with my new full-time job, which was recovering and getting better. Originally told it would take up to 8 weeks for recovery, even that in my opinion was not enough time. The time seems to go very quickly with ups and downs. Even though my recovery was going well, some days you have fatigue and just do not feel all that well. Every day is a new opportunity to try to do a bit more from the previous day.

My adjuvant chemotherapy program started 4 weeks after my surgery and continued for another 3 months. While this was physically draining, I was positive that my outcome was going to be good. The best words I heard were 2 weeks post-surgery, when my surgeon called and told me the good news that the pathology reports indicated that it appeared that all of the cancer was removed and the prognosis was good. I feel very strongly and believe that patients should not be told that they are "now cancer free!" but to be somewhat guarded in the interpretation of this statement. Being positive is good, but being realistic in expectations and hopeful is better in my opinion.

Recommendations

Most of my recommendations for improvement with ERAS have to do with communications. I can break it down into three specific areas for clarification: upon diagnosis, preparing for surgery, and at the hospital.

Upon Diagnosis

We need to be speaking to patients about ERAS and the benefits sooner in the surgical journey process. Since my surgery, I have had the opportunity to speak to a number of colorectal cancer patients in my role as a patient advisor. It is quite surprising that many of them did not remember ERAS even being mentioned until they were in the hospital in their wards post-surgery. How can that be? As I previously mentioned, once a person hears they have cancer and need treatment/surgery, they often do not have the capability to hear or process anything next. While I realize the time of diagnosis may not be the optimal time to bring up ERAS and the benefits to participate in this program, leaving it until the Pre-Admission clinic is much too late. We need to speak to the patient at every opportunity prior to surgery about ERAS, whether it be in the oncologist's office, radiation treatment appointments, and meetings with surgeons and as well with family doctors. The more we discuss this and the benefits that both the patients and healthcare system will derive, the better understanding for the patients and hopefully the greater uptake of the program.

There absolutely needs to be multiple touch points where ERAS is spoken about, especially for us men and especially for cancer patients. What I found extremely helpful in all of my appointments was to always have a second person with me at the appointments. This is where having your own personal support team is valuable. Why? Patients often hear different things than the caregiver/support person hears. Every appointment from time of diagnosis till well after my surgery was attended with a support person (mainly my wife) with myself at all times. Many times, my wife and I discussed our appointments like a meeting debrief afterward, and we both heard different words spoken and different meanings of the conversations. It also holds true that cancer patients going through chemotherapy have what is called "brain fog" or "chemo fog," which also factors in when understanding or retaining details.

Preparing for Surgery

It helps that patients need to be their own self-advocates. Oftentimes, I have heard from patients that they do not fully understand what is going on, or feel their treatments are not going well, or they are angry with the medical system. It often comes from poor communication and perhaps a lack of self-confidence. Patients need to know they are the center of their medical and personal teams. Patients are to be encouraged and reminded to ask questions, as well as to be asked questions by their healthcare team. If a person is capable and has support, then as a patient, they can be encouraged in their own accountability toward their wellness program. There is an old saying, "Those that fail to plan, plan to fail." This resonates with me, as I did have a plan, followed it, and executed it to the best of my abilities. Nobody knows the patient better than the patient themselves. We all want the same thing! We all want to live long and have a normal and productive life after treatment and surgery. Who would want the un-enhanced surgery? We as patients need to take matters in our own hands and learn as much about our diagnosis, treatment options, and enhanced recovery after surgery options and then create a path on how best to meet our goals. Patients will be a lot better off if they spent the time and energy investing in their own preparation for surgery. This pays off dividends from a physical and mental standpoint.

Exercise often and frequently prior to surgery. Walk, walk, and then walk some more. Invest in your own physical and mental well-being! I cannot stress enough how important it is to get your body into the best shape possible going into surgery treatment. Change to a high carbohydrate diet prior to surgery. Not only does eating a nutritious meal taste good, it is good for your body and mind to be ready for what lies ahead. Seek programs such as mindfulness, meditation, and yoga, even if you do not understand them or think it will help or think it's not for you. What have you got to lose in trying new things? I too was skeptical prior to beginning my meditation practice, but now I often say, "It sucks to have gotten cancer, but it has shown me many other beautiful and more important things in life."

At the Hospital Immediately After Surgery

This is where all the pre-planning and preparation pays off. By learning and doing self-research about ERAS, there will be little to no surprises about what is expected on the patient's part, once the surgery is done and recovery time begins. Yes, often there is pain, nausea, and other factors that come into play, but we need to have the will and determination to get out of bed as soon as possible after surgery. Exercise by walking helps not only the body but clears the mind as well. Moving more gets your digestive system working faster, prevents blood clots, and provides a wealth of other benefits. Eating as much nutritional foods as possible is also highly recommended. I have not heard one patient say that they have loved the food they were served in the hospital. Nobody really tells you, but there is no reason why you cannot have

someone on your personal support team bring you the food you enjoy and are accustomed to in the hospital. I was very fortunate that my daughter, who is a chef, brought me homemade turkey soup and sandwiches in the hospital during my recovery. Our ward had its own patient fridge next to the water station where we could keep our food and then heat it up in a microwave. The night of my surgery, a friend brought me takeout from a local restaurant that was fantastic. Again, by being a self-advocate and having support will help with these matters.

It is also vital that the patient follow all ERAS recommended guidelines, from drinking plenty of fluids, chewing gum, walking around the hospital ward, eating, and resting. Supplement the hospital food with nutrition drinks and with our foods we often eat at home. We as patients need to remember that it is our job to be informed and get better. The sooner the better. Also highly recommended is to reduce or alleviate the pain medications as soon as possible. Yes, pain is real and needs to be dealt with, but all too often it is used as a crutch. We all know about the opioid crisis that is among us, especially in North America. The less dependent we are on opioids or other pain medications, the better off we will all be. Mindfulness also plays a big part for dealing with pain management without meds. Use an ERAS diary to log your daily activities and goals. You'll be surprised as to how this helps with you starting to feeling better. Last, but not least, do your breathing exercises with an incentive spirometer if one is available.

At Home Post-Surgery

To quote the movie *The Wizard of Oz*, there truly is no place like home. It is often said, you do not go to a hospital to get rest. This is best done at home. Peace and quiet help the body and mind regenerate and recuperate faster. After my surgery, I was quickly gaining my strength back by going for multiple walks around the block daily with my dog. Yes, I had to be careful especially if the sidewalks were icy and slippery, but the fresh fall air did wonders to my body and mind. My goal, as mentioned earlier, was to be able to golf after 3 months of my surgery, and exercising, eating well-balanced and nutritious meals, and getting plenty of rest was the strategy. I continued my breathing exercises with the spirometer until I was back to the normal levels I was prior to surgery. Within a week of discharge, I was practicing yoga nidra (mostly breathing exercises and slow body movement) and continuing with my Mindfulness-Based Cancer Recovery program. When discharged, I was given a prescription for pain medication, which I rarely used at all, and within 2 weeks stopped using all pain meds at all. My advice to other colorectal cancer patients recovering from surgery is to think and act like a turtle. By that I mean, go slow and methodical in everything you do. Do not try to rush your recovery but take it easy. Your body is an amazing vessel and will let you know if you are exerting yourself too much. The weeks of preparation before surgery with ERAS greatly paid off, as I was able to recover very quickly without any complications or readmittances. By working on exercising (walking and yoga) and practicing mindfulness, I was quickly getting back to the same way of life I experienced BC (before cancer). Yes, my physical body was different in that I had my plumbing rearranged with my new colostomy, but once I found out I could continue leading a productive life and continue doing the things I loved, such as golfing and hunting, meant the world to me and they still do to this day.

Post-surgery, while I did have follow-up appointments scheduled with my surgeon and family doctor, it would have been nice if the hospital also followed up with me afterward to see how I was doing. A simple phone call would have been nice to receive. If only we could pass on the good word about ERAS to other patients so that they too can experience what I did. ERAS played a huge role in my preparation for surgery and my excellent recovery post-surgery. Without ERAS, no doubt I would not have been discharged as fast as I did, nor would I have felt as good as I did. Someday, it won't be called enhanced recovery after surgery and instead just be called surgery. Who would want the unenhanced version anyway?

Six weeks post-surgery, I was invited to speak to an ERAS symposium in Calgary with respect to my experience with ERAS. Since then I have spoken at several other conferences expounding on the virtues of ERAS and how we can all benefit from following the simple guidelines. Today, at every opportunity, I speak to other patients and clinicians about ERAS, in my role as a Patient Advisor with the Surgery Strategic Clinical Network within Alberta Health Services (AHS) and as co-chair of the Patient Engagement Reference group at AHS on ERAS.

My goal of being able to golf within 3 months of surgery was achieved! A few adjustments needed to take place, and I invented a new Stoma Swing for golfing to compensate for my new body. My wife and I had a wonderful and relaxing holiday that winter in Mexico. I have never looked back and am to this day golfing my usual 100 rounds per year. It has now been 3 years post cancer/treatment, and I am feeling fantastic. I continue to exercise frequently and practice mindfulness daily. Life is too short to not enjoy doing the things you love and being with the people you love.

Part VII

Safety and Quality Improvement in ERAS

Measuring Outcomes in ERAS

34

Emma L. Court, Caroline Boulind, and Nader K. Francis

Overview

Enhanced recovery after surgery (ERAS) programs are multidisciplinary clinical pathways, aimed at reducing the postoperative stress response, thereby accelerating recovery in surgical patients [1–3]. These pathways were initially developed with the intention of improving the in-hospital recovery of colorectal surgical patients [4], but recently there has been increasing interest in the longer-term recovery of patients cared for on these pathways. Traditionally, the success of ERAS has been assessed using clinical outcome measures, such as length of stay (LoS), complications, and readmission, but these measures incompletely reflect patient experience and whole functional recovery [1, 5]. A key paradigm shift within the ERAS program is the move toward a patient-centered approach to assessment of effectiveness. This chapter aims to outline measurement of ERAS outcomes, to explore why this approach is important, and to discuss various tools described in the literature used to measure the effectiveness of ERAS.

Measuring ERAS

True measurement of recovery is challenging, as it is a complex construct encompassing many dimensions of physical, psychological, economic, and social healthcare [6]. Recovery can also be interpreted differently between healthcare systems and can be subjective. For instance, clinicians are frequently more interested in short-term and in-hospital recovery measures, such as LoS and complications. In contrast, ERAS® Society guidelines emphasize the importance of auditing compliance with the different ERAS components [1], while patients equate recovery with a return to their normal activities [7]. The latter is a long process that takes place in the weeks and months after discharge.

Why Do We Need to Measure Outcomes of ERAS?

Since recovery is such a complex process, why do we need to measure the outcomes of ERAS? There are several compelling reasons to assess ERAS and its outcomes [8]:

1. *Measuring effectiveness*: Demonstration that a program is effective or, otherwise, is vital to identify areas for improvement, to enhance efficacy, and thus to afford patients the maximum benefit possible from the process.
2. *Identifying variabilities or inconsistencies in practice*: Collecting information regarding practice variation identifies ERAS programs that are effective and those that are less so. This is not only important for quality assurance of service provision but also for identification of practices that need development.
3. *Demonstrating value to existing and potential funders*: Healthcare systems are under financial constraints globally; thus it is important to demonstrate to funders and managers that a program works, is acceptable to patients, and can be achieved within a realistic budget.
4. *Promoting research and development:* Outcomes measurement facilitates improved understanding of individual programs. Measuring ERAS outcomes in clear, effective ways can identify areas requiring further study, thus promoting evidence-based practice for the overall benefit of patients.

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Measuring Process Versus Outcomes

Program evaluation can be defined as the systematic application of social research procedures for assessing the conceptualization, design, implementation, and utility of health or social interventions [9]. The term includes a range of activities, which have the potential to specifically and with more certainty demonstrate that the results of a program are attributable to the program itself and no other factors [10].

Measuring the quality of healthcare delivery plays a key role nowadays. Quality metrics, including reimbursements, with incentives to provide optimal service, are becoming popular [11]. Donabedian described a model of quality metrics, which has been widely accepted [12]. This model describes three categories of quality metrics: structure, process, and outcomes. Structural measures refer to the organizational structure, human resources, and materials required to provide healthcare. Within ERAS, this could apply to team functioning and organizational resources, to ensure ERAS is well implemented. Process measures refer to the actions performed in order to provide or receive healthcare, which outlines adherence to ERAS elements. The key concept is that ERAS elements work collectively to attenuate surgical stress response and maintain postoperative physiological function, thereby improving outcome measures [13].

A number of studies specifically examined effects of ERAS on the surgical stress response and immune function. Although these are not outcomes *per se*, they may explain the effect of ERAS, particularly the observed long-term survival benefit. In an *ad hoc* analysis of the LAFA trial, Veenhof *et al*. found that preservation of immunocompetence, assessed by monocyte human leukocyte antigen-DR isotype (HLA-DR) expression, interleukin 6 (IL-6), C-reactive protein (CRP), and growth hormone (GH) levels, may protect against seeding of tumor cells [14].

Variable terminology used in relation to ERAS and outcomes measurement in general can confound their assessment. Outcomes measurement is "a systematic way to assess the extent to which a program has achieved its intended results" [9]. A set of observations, frequently referred to in ERAS literature, is the measurement of adherence to the ERAS protocol. Understanding how well protocols are used and where deviations occur is important for the identification of weaknesses in the processes of care. However, measurement of such factors should not be considered outcomes of ERAS. There is a need to change the emphasis of measurement, from caregivers' perspectives into a patient-centered process.

How Are ERAS Outcomes Currently Assessed in the Literature?

Over the past 20 years, there has been a paradigm shift in measuring outcomes following surgery. In addition to clinically oriented outcomes such as LoS and complications, attention to measuring patient experience has been growing over the past few decades. Patient-related outcomes (PROs) are designed to directly measure patient-specific health outcomes, including general health, which may be affected by interventions. These include endpoints such as symptoms (pain, nausea, fatigue), functional health status (return to activities, physical activity levels), or health-related quality of life (HRQoL). A core set of outcomes is an agreed minimum group of outcomes that should be measured in the evaluation of a particular health condition or treatment, prioritized by the relevant stakeholders, which include both clinical outcomes and PROs [10].

As a result of the complexity of ERAS programs and difficulties in the measurement of recovery, a large number of outcomes have been described. In a systematic review by Messenger *et al*., a total of 159 different outcomes were reported. Of these, however, only LoS, complications, and readmissions were widely used [15]. Although this review focused on the prediction of ERAS outcomes, emphasis on outcomes definition was also explored. Twenty studies defined morbidity, and ten studies graded the severity of complications using the Clavien-Dindo system. A definition of LoS was provided by 20 studies, stating time from the date of surgery until discharge, except when readmission was incorporated, or time until the patient was deemed medically fit for discharge [16].

In another systematic review, Neville *et al*. identified 38 studies comparing ERAS with traditional care after abdominal surgery [17]. From these 38 studies, 23 outcome measures were identified. Of these, 10 were biological or physiological outcomes, 4 were PROs relating to symptoms, and 11 were measures of functional status, including quality of life (QoL) scores. These are summarized in Table 34.1.

Assessments of functional status include outcomes used to assess recovery in the longer term after surgery. Seventeen studies reported on outcomes post-discharge. However, only two studies reported outcomes up to 60 days and one study up to 90 days, and ten studies did not report the duration of follow-up. Twenty-four studies reported outcomes only to 30 days post operation. Such a short duration of follow-up suggests study outcomes are surgeon- or hospital-centered, rather than considering the patients' perspectives.

Of the studies that did report symptom status, only eight did so postoperatively. Functional status was assessed in multiple ways, and LoS (considered a proxy measure of functional status) was reported in all but one of the studies. Measures of patient mobility were reported in 16 studies, which was assessed in a number of ways. These included "time spent out of bed," "time spent ambulating," "pedometer recordings," and "proportion of patients who walked on a given postoperative day" [17].

When considering recovery from the patient perspective, the ability to perform activities of daily living, both basic and

Table 34.1 ERAS outcomes and their measurement

Identified outcomes	Definition, measurement technique, and/or instrument
Biological and physiological variables	
Postoperative complications	Multiple definitions
Return of bowel function	Passage of gas Passage of stool
Time to tolerate diet	Tolerance of oral intake (fluid or solid meals)
Pulmonary function	Spirometry
Immunological measures	C-reactive protein Interleukins Tumor necrosis factor α (alpha) HLA-DR expression on monocytes Lymphocyte flow cytometry
Stress response	Cortisol Prolactin Growth hormone Insulin resistance
Nutritional indices	Albumin Nitrogen balance
Changes in body composition	Bioimpedance Absorptiometry
Muscle strength	Hand grip Lower extremity strength
Resting energy expenditure	Indirect calorimetry
Cardiovascular function	Treadmill testing
Symptom status	
Pain	Visual analogue scale Verbal response scale McGill pain questionnaire
Fatigue	Visual analogue scale Verbal response scale Identity-Consequence Fatigue Scale Hours sleeping
Nausea/vomiting	Self-report Verbal response scale
Anxiety/depression	Hospital anxiety and depression scale
Functional status	
Length of hospital stay	Number of days
30-day readmission	Number of patients readmitted within 30 days of discharge
Mobilization	Time spent out of bed Time spent ambulating Pedometer Proportion of patients walking on a given day Time to reach independent mobility
Ability to perform activities of daily living	Basic activities of daily living questionnaire Instrumental activities of daily living questionnaire Activities of daily living subscale of the Identity-Consequence Fatigue Questionnaire
Return to work	Unclear
Cognitive function	Roth-Hopkins test
General practitioner visit	Unclear
Need for psychological support	Questionnaire
Discharge to rehabilitation facility	Patients discharged to facility other than their own home
General health perceptions	SF-36 general health subscale EORTC overall QoL scale
Overall QoL and health aspects of QoL	Spitzer index Quality of recovery score Cleveland Clinic global quality of life questionnaire SF-36 general health subscale Gastrointestinal quality of life index EQ-5D EORTC QLQ-C30 and QLQ-STO22 Surgical recovery scale

HLA-DR human leukocyte antigen-DR isotype, *SF-36* Short Form 36, *EORTC* European Organisation for Research and Treatment of Cancer, *QoL* quality of life, *EQ-5D* EuroQol Group 5-level questionnaire, *QLQ-C30* Quality of Life Questionnaire-Core 30, *QLQ-STO22* Quality of Life Questionnaire-Stomach

instrumental, is an important measure. This was assessed in only 2 of the 38 studies. When functional status was assessed, it was measured during the inpatient stay in all cases, but only eight studies measured post-discharge functional status outcomes.

Quality of life was measured in seven studies using eight different assessment techniques. Five of the seven studies measuring QoL did so at three time points (baseline, intermediate, and late). However, despite QoL assessment tools being measures of long-term outcomes, none of the studies used them after 30 days post-discharge [17].

Many studies included in the review reported measures of processes of care. These included many aspects of adherence to the ERAS pathway, including removal of catheter, use of intravenous fluids, instigation of oral diet, etc. These are interesting and important to know but should not be considered an outcome of ERAS. Rather, they may help to explain differences or changes in outcomes and can be used to improve implementation of the ERAS program.

When to Measure ERAS Outcomes?

The aim of ERAS is to improve patient recovery throughout the entire process. An optimal measure of recovery should address the whole patient journey (Fig. 34.1). A holistic approach into measuring the whole recovery process is therefore required. This should encompass measuring early recovery as reflected by patient symptoms such as pain, nau-

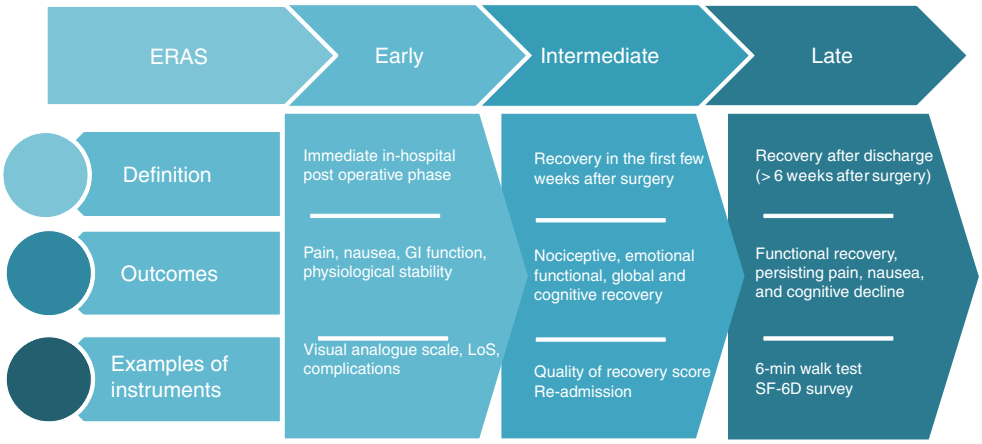

Fig. 34.1 Measuring ERAS outcomes. *GI* gastrointestinal, *LoS* length of stay

sea, and fatigue. Later measures of recovery are also essential including QoL and the ability to perform activities of daily living. It has been observed in the recovery of patients over the age of 60 years undergoing major abdominal surgery that it takes up to 6 months post-surgery to regain the ability to perform instrumental activities of daily living and baseline grip strength [18]. This recovery cannot, therefore, be adequately assessed with outcome measures observed at less than 30 days. Even ambulatory procedures can require up to 1 month for full recovery [19]. This approach should also be taken into account when organizations are measuring the financial impact of recovery to consider the whole recovery process.

Recognizing the limitations of the ways in which outcomes for ERAS have been assessed to date, Feldman *et al.* have recommended a core outcomes set for studies assessing ERAS programs [20]. These have recently been developed for a number of specialty areas, after recognition of inconsistency in the way outcomes are measured and the need for standardization between investigators. The use of a core outcome set relevant to the area of study allows synthesis of data from multiple studies as well as recognition of important areas for investigation. Feldman's core outcomes set breaks down outcomes into two chronological categories: (1) those measured in the intermediate phase of recovery (in hospital) and (2) those in the late phase of recovery (after discharge). The outcomes of interest, divided by phase of recovery, naturally reflect the interests of the various stakeholders at different points in the patient journey. The intermediate phase outcomes are focused more on physiological outcomes, symptoms, processes of care, and adverse events. Conversely, the later phase outcomes are more related to the interests of the patients, measuring functional recovery, quality of life, and return to normal activities. Importantly, appropriate tools have been suggested for use, which have been validated in the context of post-surgical recovery. It is important to note that these core outcomes have not been developed using a standard consensus process and act only as a starting point for such an undertaking. However, they will be used as the basis for discussion here.

Classification of ERAS Outcomes

Recovery can be classified into three phases: early, intermediate, and late. The early phase of recovery, defined by Bowyer et al., encompasses factors important for hospital discharge, such as pain, nausea, gastrointestinal (GI) function, and physiologic stability. Intermediate recovery includes the first few weeks after surgery, which involves nociceptive, emotional, functional, and cognitive recovery. Late recovery is defined more than 6 weeks after surgery, focusing on functional recovery and any persistent symptoms or cognitive decline [21].

Outcomes in the Early Phase of Recovery

Measuring recovery in the early phase can be challenging, due to the complexity of the recovery process immediately after surgery. Efforts to quantify this include measuring LoS and complications, but these are products of the recovery process. A number of studies focused on measuring patient symptoms such as pain, nausea, fatigue, and emotional symptoms such as anxiety and/or depression. A visual analogue scale (VAS) has been used to measure postoperative pain and fatigue [17]. Identity-Consequence Fatigue Scale and the "need for sleep" have also been used to measure fatigue.

Pain Control

The measurement of pain in studies of ERAS would be classified as part of symptom status, which also included fatigue, nausea/vomiting, and anxiety/depression in the review by

Neville [17]. Pain was the most frequently reported symptom outcome, included in 16 of the 38 studies in the review. It is the only symptom status outcome suggested as part of the core outcomes set. Fatigue, nausea/vomiting, and anxiety/depression were reported in nine studies, six studies, and one study, respectively. The majority of studies reporting pain used a visual analogue scale to do so (13 of the 16 studies). Verbal response scales were used in three of the studies, and one study used a questionnaire in addition to the VAS. The use of VAS to assess pain in postoperative patients has been validated as a ratio measure of both chronic and acute pain and can be used to compare one-off pain scores between groups, as well as monitoring changes in pain score over time [22]. Only eight of the studies reporting symptom status included post-discharge assessments—again highlighting the focus on surgeon- and/or hospital-focused outcomes. In addition to recommending the use of VAS for pain assessment, Feldman *et al*. go further, suggesting it is measured not only at rest but also during coughing and exercise [20]. This would allow further discrimination of pain status, identifying the point at which patients are pain-free during activities required during everyday life rather than simply when lying in bed.

Gastrointestinal Recovery

This outcome measure has been reported using many assessment methods, frequently including recommended approaches. Validated measures of bowel function include tolerance of oral food and the passage of stool or flatus [23]. The use of the first of these should be carefully described in study protocols to clarify what is meant by this term, for example, three full meals per day, one meal, soup, etc. It should also be made clear how, and by whom, these outcomes are measured—documentation by the patient or observation of meal times by an assessor, for example. Future development of a core outcomes set by formal consensus methods should include identification of the most appropriate measure of GI function in this patient group. From a patient perspective, it is likely that normal GI function would be described as the ability to eat and drink normally, along with normal bowel function. However, it is probably unnecessary for patients to reach this level prior to discharge, and this fundamental difference should be recognized.

Complications

Complications have been frequently assessed in ERAS trials, with 35 of the 38 studies in the above review including complications in their outcomes [17]. However, only five studies categorized complications using a recognized, validated system such as the Clavien-Dindo scale or the comprehensive classifications index [17]. It is recommended that such tools are used when reporting complication outcomes, because it allows results from multiple studies to be easily compared and combined.

Length of Hospital Stay

All but one of the studies in the review by Neville *et al*. reported LoS as an outcome [22]. Length of stay has direct impact on costs for the hospital (and depending on the healthcare system, also incomes). LoS is also frequently reported as a proxy measure for overall functional status. Fitness for discharge implies an ability to perform at least basic activities of daily living, as well as satisfactory pain control and GI function. This information can also be used in calculation of the economic impact of an intervention, such as bed usage, etc. As a result, LoS is frequently reported, although these data have been difficult to synthesize in reviews due to data heterogeneity. For example, it is not always clear how fitness for discharge is defined, and this does not always coincide with the actual discharge date, due to other confounding factors such as the need for a temporary care package or placement in a community hospital. For this reason, it is important that authors clearly define *a priori* the criteria used to assess fitness for discharge. Ideally, these criteria should be defined during a consensus process to identify core outcomes for ERAS, enabling more homogeneous data to be collected across multiple studies. In addition, collection of data regarding fitness for discharge as well as total hospital stay facilitates better understanding of the implications of non-clinical delays in discharge among post-operative patients.

Outcomes in the Intermediate Phase of Recovery

Assessment of recovery in the intermediate, in-hospital phase addresses the interests of both clinicians and patients. All of the aforementioned outcomes of the early phase have also been used to measure recovery after discharge. The suggested constructs to consider assessing include complications, GI recovery, pain control, LoS, and global recovery.

Global Recovery

Global recovery has been recommended as an outcome measure for ERAS in the intermediate phase [20]. Measures of global recovery assess recovery from the patient's perspective, focusing on aspects important to patients. Myles *et al*. have validated a 40-point questionnaire to assess global recovery in post-operative patients (QoR-40) [24]. The questions were developed through discussion with key stakeholders—including patients and their relatives, nursing staff, and clinical staff—who identified key factors they felt important in post-operative recovery. These included emotional state, physical comfort, psychological support, physical independence, and pain. The authors found that patients were able to complete the questionnaire in less than 10 min and did not find this too onerous. Patients were asked to rate their

symptoms in each of the domains using a 5-point Likert-like scale. One of the strengths of this score is the combination of multiple different assessments of recovery important to both patients and clinical staff. Evaluation of the psychometric properties of the QoR-40, from 17 studies in which it was used, concluded that it was a suitable measure [25]. However, the QoR-40 was designed to reflect early recovery and normalizes within days to weeks [26]. For this reason, it is suitable for measurement of recovery in the intermediate phase only, as suggested by Feldman *et al*. [20].

A review by Bowyer *et al*. identified 11 instruments for the measurement of postoperative quality of recovery [21]. The Postoperative Quality of Recovery Scale is a newer tool that emphasizes cognitive functioning [27], but other measures, such as the Abdominal Surgery Impact Scale [28], were not included in reviews. This highlights difficulties in this area, where variable definitions of recovery hamper identification of scales in reviews and data synthesis. Rigorous assessment of the level of validation for each measure could guide investigators as to the optimal utility of each tool.

Outcomes in the Late Phase of Recovery

Reporting on late recovery in general has been less frequent in the literature compared to the early phase. Recommendations included in Feldman's core outcomes set comprise assessment of functional status, pain control, HRQoL, and readmissions [20].

Functional Status

Measurement of functional status is described by Feldman *et al*. as "activities and participation." They suggest the use of validated questionnaires as well as measurement of the time to return to work and to specific pre-defined activities, which would need to be identified during a formal consensus activity. Interestingly, they do not include measurement of mobilization in assessing functional status. This may be due to a lack of validated mobilization measures. This is highlighted by infrequent reporting of mobilization in Neville's review [17]. Despite early mobilization being considered an essential component of ERAS, it was reported in only 16 of the 38 studies. This was measured in a number of ways, including time spent out of bed or ambulating, pedometer recordings, or the proportion of patients who walked on a given postoperative day. The time taken to reach independence in mobilization had also been used by a number of studies. This was defined as the ability to mobilize to the bathroom, or a predefined distance, without aid, though some of the studies did not include a definition. This example clearly illustrates the current problem with synthesizing data from ERAS studies, with outcomes based on non-validated measures of mobility.

Two studies assessed activities of daily living (ADLs) as the time taken until patients were capable of self-care. Some used validated questionnaires, including the Identity-Consequence Fatigue Questionnaire. In their core outcomes set, Feldman *et al*. include examples of validated measures that could be used to assess activities and participation [20]. These include the CHAMPS (Community Healthy Activities Model Program for Seniors) tool [19], which comprises 41 questions estimating the time spent on a variety of activities, from light to strenuous intensity, over the course of a week. CHAMPS has been validated for assessment of postoperative recovery in patients aged between 20 and 84 years of age [19]. A second measure, the Instrumental Activities of Daily Living Scale (IADLS), requires patients to score their ability to perform various tasks. They select one of four levels of functioning, which are well defined, ranging from fully independent to completely unable to complete the task. It has been demonstrated that it can take up to 6 months for patients to regain baseline level of functioning in IADL and this measure can be used to monitor progress [20].

Pain Control

As well as being useful in the intermediate phase of recovery, assessment of pain can be useful later in the recovery process. It is suggested that pain be measured using VAS at rest, during coughing, and exercise, as recommended for the early part of recovery. This has been discussed earlier in this chapter.

Health-Related Quality of Life

Health-related quality of life measures can be useful tools in the measurement of recovery. The Short Form 36 (SF-36) is widely used and can be used in the assessment of surgical outcomes. It includes 36 items and can be divided into eight domains including physical functioning, physical role, bodily pain, vitality, emotional role, mental health, social functioning, and general health. There is existing evidence that six of the eight domains and the physical component summary score can be useful in the assessment of recovery after colorectal surgery [29]. Measures of quality-adjusted life years, which can be assessed indirectly using SF-6D, can also be used. It is important when choosing instruments to measure HRQoL that they are considered in the context of disease and timeframe, to ensure the correct instrument is used. It is also important to remember the limitations of such measures. Changes in perception and expectation, as a result of disease processes and treatment, can also introduce changes in reporting, which make interpretation difficult. For example, after a diagnosis of cancer, a patient may report a relatively poorer HRQoL than prior to the diagnosis. Following surgical treatment, the same patient may feel very positive and hopeful, leading them to report an improved HRQoL despite the immediate post-operative consequences

of surgery producing an objective deterioration in health. This is referred to as a shift of internal standards ("recalibration"), values ("reprioritization"), or conceptualization ("reconceptualization").

In Neville's review [17], only 2 of the 38 studies included reports of general health perceptions, reported as the general health perception subscale of the SF-36, or the overall QoL scale of the European Organisation for Research and Treatment of Cancer (EORTC) QoL questionnaire [17].

Hospital Readmissions

Readmission following surgery is commonly reported in trials, with 29 studies in the review reporting this outcome. It is classified by Neville *et al*. as a functional status outcome, reflecting poor functional status culminating in the need for readmission [17]. More recently, focus has shifted toward the impact of hospital readmission following discharge, although little has been reported on this aspect of recovery. Healthcare costs in the UK and the USA are growing exponentially [1, 5, 6], and as a result, readmissions to services within 30 days of discharge are no longer reimbursed, thus providing institutions with an incentive to strive for successful discharge. In the USA, the Patient Protection and Affordable Care Act of 2010 made hospitals financially accountable for 30-day readmissions [1].

In addition to the added cost of readmission to the institution, a patient's unplanned return to hospital further limits healthcare resources. For each patient readmitted, there is an opportunity lost to treat another patient in need of care. Readmission also impacts negatively on a patient's QoL and their overall healthcare experience [7]. This has prompted the use of readmission as a surrogate marker of poor-quality patient care. Consequently, reducing readmission has become a key healthcare target, both in the UK and USA [9, 10, 15].

A study examining factors that predict readmission after colorectal cancer surgery defined readmission as occurring within 30 days of discharge and directly related to the index admission. It was demonstrated that poor compliance with an ERAS protocol and the use of neoadjuvant therapy independently predicted 30-day readmission. Furthermore, patients who received neoadjuvant therapy experienced a longer LoS and were over four times more likely to be readmitted within 30 days of surgery, compared to patients who did not receive neoadjuvant therapy [30].

Aside from the outcomes suggested by Feldman *et al*. in their suggested core outcomes set [20], there are other outcomes that may be of interest to individual investigators, in addition to those discussed previously.

Cognitive Function Testing

Surgery has been shown to negatively affect cognitive function, which can potentially be permanent, especially in older patients [31–34]. Post-operative cognitive impairment involves deterioration of function, compared to population norms, and can present as either acute delirium or cognitive dysfunction. Measurement of cognitive recovery necessitates comparison with pre-operative baseline. Cognitive impairment and non-cognitive recovery are interlinked [35, 36]. Both short- and long-term cognitive impairments are associated with long-term mortality, with cognitive dysfunction at discharge being associated with mortality at 3 months. Furthermore, ongoing cognitive dysfunction at 3 months is associated with mortality 9 months later [36]. This is worse among older patients, as cognitive impairment is more persistent in this group. Identification of cognitive impairment is important in post-operative patients in order to minimize the associated morbidity and mortality. Hence, assessment of cognitive recovery should be carried out at multiple post-operative time points, and there are a number of tests available. The Confusion Assessment Method (CAM) is widely used and applicable to post-operative patients [37]. More specifically, Basse *et al*. used the Roth-Hopkins test for cognitive function in the early publication of ERAS [38].

Long-Term Impact of ERAS

The long-term impact of ERAS programs has been evaluated by a number of studies. In their study of 911 colorectal cancer patients, Gustafsson *et al*. demonstrated that adherence to ERAS protocols of greater than 70% was associated with better survival at 5 years. Significant independent perioperative predictors of increased survival were avoidance of fluid overload and oral intake on the day of surgery. In a prospective study of 845 patients by Francis *et al*., a beneficial association between ERAS laparoscopic surgery and 5-year overall survival was reported [30].

Limitations of Measuring Outcomes

It is important to understand that measurement is simply a means to collect information to support a continuous process of service improvement. Measurement should not be seen in itself as an aim or a target, as there are certain limitations that need to be considered.

"Soft outcomes" may be more important than the movement toward metrics permits. ERAS is based on multidisciplinary interactions. Building relationships between different members of the ERAS team is an important result of activities undertaken when implementing ERAS, and this can be hard to measure.

Different healthcare polices and funding strategies need to be considered when measuring ERAS outcomes. For instance, in certain healthcare systems, there may be financial penalties for early discharge, which inhibit healthcare

professionals from discharging patients early [39]. In this instance, focusing on LoS can provide an incomplete picture of ERAS of program effectiveness.

Measuring outcomes is a continuous process that needs time to accomplish. Relying on a snapshot of outcomes at a single time point can be misleading, because the data may represent part of a learning curve or sustainability issue. Measuring ERAS should be considered over a long period of time. This must be balanced with activities that contribute to systemic changes that may take years or decades to realize. Moreover, outcome measurement is about the past. Decision-making (budgets, policy, etc.) is about the future, where dynamic environments and other influencing factors may be constantly evolving.

Ultimately, outcome measurement is a surrogate marker that cannot take the place of clinical judgment and decision-making. The analysis and interpretation of this data cannot be replicated by statistical analysis tools. Critical thinking skills must be applied to the information gathered in the outcome measurement process in order to draw meaningful conclusions regarding the impact of individual components of the ERAS program on patient care.

Conclusion

ERAS outcomes measurement is complex and can be challenging. It must be patient centered and considered as a long-term, dynamic process that can be used to inform further development of services on the whole patient journey. Selection of appropriate outcome measures is vital, to allow reliable interpretation of results. Problems arising from significant data heterogeneity from existing studies make it difficult to synthesize the literature. This might be overcome in the future by the development of a core outcomes set for trials assessing ERAS, with formal and structured definitions of each of the outcomes of interest as well as suggestion of appropriate tools for their measurement.

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Measurement of Recovery Within ERAS

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Andrea Bowyer and Colin F. Royse

What Does It Mean to Recover?

Obtaining quality of recovery is an abstract construct that is the ultimate goal of each perioperative experience. Recovery assessment has progressed from the unidimensional historical construct focused purely on that which determined safe discharge from theater [1] to a multidimensional construct that encompasses functional recovery, symptomatology, cognitive function, and patient-reported outcomes (PROs). Historical indicators of poor recovery have primarily addressed that which is important for hospital discharge and resource utilization: basic functional assessment, the presence or absence of adverse symptomatology (pain, nausea, etc.) [2–8], emotional and psychological distress [6, 7, 9–11], or patient dissatisfaction [6, 7, 12–14]. Modern recovery, however, is best viewed as a multidimensional construct extending beyond the immediate postoperative period and is best defined by outcomes that are important to both clinician and patient.

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The Temporal Nature of Recovery

Integral to the concept of recovery within ERAS (Enhanced Recovery After Surgery) is the notion that recovery is a multidimensional and continuous process that occurs over sequential time periods [15–17]. The recovery trajectory commences with an abrupt decline from function (temporally associated with surgical injury or trauma), which precedes a time-dependent restitution of function and well-being toward a plateau that may be similar to, or different from, the patient's own preoperative baseline. Recovery assessment is thus inherently a comparison of a patient's postoperative function to that of a preoperative performance—ideally their own—with an assessment of the magnitude of this change to determine its clinical significance.

ERAS has traditionally defined three recovery time periods: early, intermediate, and late recovery [15]. Early recovery is defined as that which is important for safe discharge to the ward (restitution of physiological parameters); intermediate recovery as that which is essential for hospital discharge (presence of adverse symptomatology [pain, nausea], basic resumption of functional activities, self-care); and late recovery as that which occurs post-hospital discharge until such time as a patient has returned to "normal activity." The two former time periods are inherently provider and institution focused and assess recovery via surrogate performance indicators that also determine resource utilization [18, 19]. Patient-focused outcomes are only assessed within the latter recovery period. Alternatively, early, intermediate, and late recovery can be defined in terms of that which is important for hospital discharge (physiological function and absence of adverse symptomatology), successful return to home (nociceptive, emotive, functional, and cognitive recovery), and return to previous level of function (poor functional recovery, persistent pain, nausea, and cognitive decline), respectively [20]. Despite discrepancies in terminology used to temporally define recovery, it is essential that modern recovery assessment tools are multidimensional and validated for repeat measures, thus enabling extended assessment of

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patients along the recovery trajectory out beyond the immediate postoperative period.

Measurement of Recovery Within ERAS Programs

Recovery assessment within the scope of ERAS programs has traditionally focused on unidimensional outcomes important for patient discharge (length of hospital stay [LOS]) and resource utilization (hospital readmission). Two systematic reviews analyzing the efficacy of enhanced recovery after surgery pathways [18, 19] revealed LOS and the presence of complications as being almost universally reported within ERAS studies, whereas patient-centered outcomes were almost universally absent. This is important given that traditional unidimensional postoperative outcome measures lack patient focus and, when used in isolation, were found in two systematic reviews to have rarely improved patient outcomes [21, 22].

A systematic review of the outcome measures used to evaluate ERAS programs [19] identified 38 studies, 25 of which were randomized control trials. LOS was the most commonly reported outcome, being reported in all but one study, and was specifically defined as the primary outcome in 18 of the studies. Other commonly reported outcomes also pertained to the immediate in-hospital period—namely, physiological parameters (25 studies), pulmonary function (5 studies), and basic physical strength (3 studies). Fifty percent of studies included parameters that addressed basic functional status, most commonly in-hospital mobility; while this has been traditionally a surrogate for readiness for discharge, it has yet to be determined whether this correlates to successful resumption of daily activities once a patient has been discharged. Cognitive assessment was included in only one study—a significant omission due to the known interplay between impaired cognitive and non-cognitive recovery and increased patient morbidity and mortality [23–25]. Interestingly, quality of life (QoL) measures were included in seven studies, but only one of these used a validated health-related QoL-specific instrument. The time periods over which recovery was assessed were predominantly limited to the in-hospital and immediate discharge period. While all studies reported on the aforementioned in-hospital variables, only 17 studies reported on variables specifically confined to post-hospital discharge. A meta-analysis of enhanced recovery programs in 5099 surgical patients [18] reported ERAS pathways to be associated with a reduced length of hospital stay (−1.14, 95% CI −1.45 to −0.88) and 30-day mortality (RR 0.71, 95% CI 0.6–0.86) but was unable to detect additional benefits due to the included studies nonuniform study design, nonuniform definitions, and low power. One of these reviews [19] called on future reporting of ERAS pathways to include both patient-centered outcomes and data that could provide context to the traditional outcomes. These reviews, along with editorials [26, 27], highlighted that while traditional outcomes of LOS and readmission rates are essential components of recovery assessment as they have direct impact on resource utilization, they lack patient focus and do not fully address the multidimensional nature of modern recovery assessment.

Concept Analyses and the Development of Modern ERAS Recovery Assessment

There has been significant discussion within the literature as to what best defines modern ERAS recovery. A concept analysis [28] concluded that the attributes that defined modern recovery were those of an energy-requiring process that culminated in the return of a patient to a relative state of normality, independence, optimal well-being, and self-efficacy. Recovery was thus defined in terms of the absence of unpleasant symptoms, re-establishing emotional well-being, and resumption of functional activities. Similarly, another concept study [29] also defined recovery in terms of absence of adverse symptomatology and restitution of basic bodily functions. A more recent concept analysis specifically addressing recovery within the ERAS framework [17] aimed to develop a conceptual framework with which to define, and hence assess, recovery post abdominal surgery. It first defined 22 recovery-related concepts, classified them according to the International Classification of Functioning, Disability and Health (ICF), and used this as the basis to determine the content validity of eight patient-reported outcome assessment tools. The four most important concepts of recovery (an energy-requiring process, an absence of pain, general physical endurance, and ability to carry out daily routine) were consistent with that reported in previous studies and emphasized recovery as the resumption of previous activities undertaken. These concept analyses are in keeping with the wider literature where patients define recovery not just in terms of restitution of basic physiological function but also in terms of their ability to return to a previous "normality," a resumption of previous life roles [30–33]. There is, however, often a disparity between traditional objective recovery assessment variables and that which is defined by the patient, as the latter is heavily influenced by each patient's individual internal cognitive framework (personality traits, coping mechanisms, and global sense of security) and knowledge regarding their expected recovery trajectory [31]. Thus, modern assessment of ERAS recovery must include both traditional parameters, such as restitution of physiological and physical function, as well as the broader nociceptive, emotive, social, satisfaction, and cognitive domains [31, 34].

Approaches to Recovery Assessment

Objective Versus Subjective Assessment

Modern postoperative recovery assessment faces the challenge of providing objective measurement of variables that by their nature are inherently subjective and of including in its breadth of assessment recovery domains that have tangible meaning to both patient and provider. Traditionally, recovery assessment was quantified using unidimensional objective measures. However, the multidimensional recovery construct has implications to both patient and provider and has required recovery assessment to include more subjective (and in particular patient-reported) outcomes.

The terms "objective" and "subjective" outcomes are entrenched within the medical literature yet lack unifying definitions. A systematic review [35] of 90 methodological publications and 200 clinical trials found there to be no unifying definition of either variable. It revealed, however, that common characteristics were associated with each. A subjective outcome was concluded to be that which is dependent in part upon an individual's judgment (be it either the patient or an observer), is patient-reported, or is a private phenomenon (measurable only by the patient). Conversely, an objective outcome was one that was independent of an individual's judgment (be it patient or an observer) and was reported and assessable without judgment by an observer other than the patient. Patient *centered* outcomes, which may be measured either objectively or subjectively, are those that hold intrinsic value to the patient [36–39]. In comparison, patient *reported* outcomes are inherently subjective as they are direct patient reports from the perspective of the patient without inference or judgment from an external observer [36, 40]. This distinction between objective and subjective variables has clinical ramifications, as subjective outcomes are by necessity unblinded and hence particularly susceptible to reporter bias and overexaggeration of treatment effect size and are influenced heavily by the patient-provider relationship [35, 41, 42].

Objective Outcomes

Clinical Performance Indicators

Recovery at the institutional and provider level has been traditionally by proxy through the use of clinical performance indicators (CPIs). The benefit of CPIs is that they are objective outcome measures that are easily reported and retrospectively audited (such as length of hospital stay) and reflect resource utilization. They have become linked to reward-based payment systems and are often used as a surrogate for quality of recovery [43, 44]. However, their utility is in detection of complications, clinical errors, and deviations from guideline adherence rather than a true measure of quality of recovery [44].

Reporting of clinical performance indicators is ubiquitous within the perioperative literature and the most common outcome reported in ERAS studies. However, an observational before-after study involving ERAS programs reported a disparity between LOS and the time a patient was deemed ready for discharge [45], with 87% of ERAS patients being discharged a median 1 day *after* discharge criteria were fulfilled. This highlights that even the dichotomous traditional outcome variable "LOS" was itself heavily influenced by social, cultural, institutional, and patient factors [46]. Of interest, a study demonstrated construct validity for "Time to Readiness for Discharge" as an alternative surrogate measure of short-term recovery [46], which aims to mitigate the impact of confounding influences on assessment of recovery. These studies emphasized the lack of collection of contextual variables (patient comorbidities and surgical complexity) with which to analyze these objective outcomes (length of stay) and recommended future studies to include these. Furthermore, a recent ERAS consensus statement advocated for traditional clinical outcomes to be routinely recorded with contextual variables such as patient case mix [47]. Another systematic review [17] concluded that unidimensional outcomes are beneficial in assessing adherence to clinical pathways and identification of sentinel events, but must be viewed in the context of confounding variables (differences in patient case mix, anesthetic and surgical complexity, measurement error or chance [43]). Importantly, when used in isolation, they are rarely associated with improved patient outcomes [21, 22]. Thus, while objective outcomes are easy to measure, only through their interpretation in a clinical context can they be true measures of the multifaceted nature of recovery [48].

Subjective Outcomes

Patient-Reported Outcomes

Patient-reported outcomes (PROs) are subjective measures that prioritize the patient's perspective as being that which is the most important at the time of assessment and are essential to the provision of high-level patient-centered care [26, 40, 49]. They are specifically adept in capturing the multidimensional and interrelated nature of recovery domains [40, 50], define recovery in terms of the patient as the key stakeholder, and ultimately optimize patient outcome through facilitating patient engagement in the recovery process [51]. PROs commonly aim to quantify more abstract concepts of recovery not traditionally assessed: postoperative quality of life, satisfaction, and personal experience of care [36]. However, PROs as surrogate measures of recovery are hindered by their inherent subjective nature, lack of validated assessment tools, and their susceptibility to response shift and recall bias [37, 40].

Patient-reported outcome measures (PROMs) are the means by which PROs are measured. PROMs were initially utilized in pharmacological and health service research but have now become commonplace in the clinical arena to the extent that they are embedded in regulatory requirements and routine clinical care reporting [36, 52, 53]. However, a systematic review identifying 22 unique PROMs for post abdominal surgery [40] reported 74% as displaying only fair or poor development methodology, with the majority being based on limited or unknown evidence. Importantly, no PROM adhered to the International Society for Quality of Life Research [38] minimum standards (internal consistency, reliability, content validity, hypothesis testing validity, or responsiveness), although the four recovery-specific PROMs did demonstrate sound content validity. In addition, PROMs were reported to be susceptible to the time delay between their reporting and the event being assessed, which directly impacted on the likelihood of both recall and response shift bias. In response, groups such as the Patient-Reported Outcomes Measurement Information System (PROMIS) and Oxford Patient-Reported Outcomes Group aim to calibrate and standardize contemporary PROMs for both clinical and research applications [38, 50, 54–56].

Response Shift and Recall Bias

Although not insurmountable, a major limitation of subjective outcomes is its susceptibility to measurement bias, in particular that due to response shift and error in patient recall. There is also the issue of from whose view the health state is measured. Recovery inherently infers that a comparison is made between a patient's postoperative state of health (or part thereof) and a preoperative control—ideally their own preoperative baseline. This "change" is a surrogate marker of recovery for that health domain being assessed, with subsequent assessment of the magnitude of this change to determine whether it is within what is expected for that recovery interval. However, change scores that are reported by the patient and those that are recorded by an observer are often disparate [37, 57]. This is in part due to recall and response shift bias.

When assessing change scores, three change scores are quantifiable, which differ in their primary state of reference and susceptibility to bias (Fig. 35.1). Conventional change (CC) scores are derived by comparison of the patient's postoperative (x_1) and preoperative (x_o) scores, with the latter being the score *actually recorded* by the patient preoperatively. CC scores infer that the most important perspective from which to measure the domain of interest is that at the time of each assessment (i.e., the preoperative score is derived from the patient preoperatively and the converse for the postoperative score). Its benefit is that it is immune to recall bias, but it is susceptible to bias due to response shift. In contrast, patient-perceived change (PPC) scores are

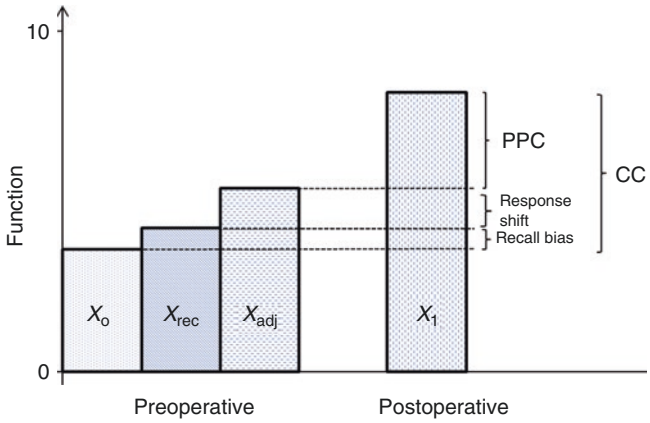

Fig. 35.1 Relationship between conventional change (CC) scores and patient-perceived change (PPC) scores. X_o, preoperative score actually recorded by patient; X_{rec}, preoperative score a patient recalls having recorded; X_{adj}, preoperative score recorded by the patient from the postoperative perspective; X_1, postoperative score recorded by the patient

derived by comparison of the patient's postoperative score (x_1) to the preoperative score that they would *now* give, *given their current postoperative perspective* (x_{adj}). PPC scores thus infer that the most important perspective from which to measure the domain of interest is from one time point (i.e., the postoperative time point is the most suitable time for the patient at which to determine *both* postoperative and preoperative scores). Its benefit is that it is immune to bias due to response shift (as both pre- and postoperative events are assessed in the context of the postoperative experience), but it is susceptible to recall bias.

Recall bias is defined as the difference between what the patient *recalls* having scored preoperatively (x_{rec}) and what they *actually* had documented (x_o). Thus, a third change score, the PPC score adjusted for recall bias (PPC_{adj}), was described [37] and is the sum of the PPC and recall bias. Similarly, response shift can be quantified as the difference between the CC and PPC_{adj} (which is the difference between the patient's x_{adj} and x_{rec} preoperative scores). This retrospective assessment of a preoperative event (i.e., how the patient rates their preoperative function from the perspective of their postoperative state) infers that past events are best compared in the context of subsequent events (the postoperative period) and from the perspective of those experiencing them (the patient). It also enables quantification of both recall and response shift bias.

Response shift was initially described within the domain of educational research and management science and was subsequently applied to the clinical arena [58] in order to quantify the normal adaptive changes that occur within a patient's internal framework in response to the passage of time and the experience of major life stressors (such as surgery of significant illness). Response shift is the alteration in a patient's cognitive framework as a result of a stressor such

that subsequent events are assessed through an altered perspective [39]. For a postoperative patient, a catalyst (surgery, trauma, or major illness) challenges a patient's internal mechanisms by which he or she accommodates the catalyst (internal behaviors, cognitive and affective processes) such that the fundamental meaning of a target construct (i.e., what it means to recover) is altered for that patient [39, 59, 60]. The mechanisms by which this alteration occurs are by one or more of recalibration (change in internal standards of measurement used to define recovery), reprioritization (change in values associated with recovery), or reconceptualization (redefinition of what it means to recover) [59, 60]. When assessing a patient's quality of recovery using CC scores, this results in measurement bias in that the same construct (quality of life, recovery) is being measured pre- and postoperatively by the *same patient* using *different (cognitive) measurement* tools. This is mitigated when the same construct is calculated using PPC scores.

Response shift thus impacts on the reliability, validity, and responsiveness of a PROM tool [58, 61, 62]. Construct validity is impacted as it assumes constant correlation between two domains of interest—a phenomenon that does not occur when two patients experience vastly different recovery experiences. Reliability is impacted as it requires that all patients share a common (and constant) frame of reference and experiences through which to view the recovery domain of interest. Thus, measurement error results when subjective outcomes are compared between disparate groups (i.e., treatment vs. control) or in the one patient but from differing perspectives (i.e., patient vs. caregiver vs. family member), as both the baseline cognitive framework and magnitude of response shift differ among patient, caregivers, and providers as a result of differences in an individual's experience, fear, focus, or internal standards [39]. Interestingly, when correcting for the effect of response shift on health-related outcome measures, there is often an increase in the treatment effect detected and a reclassification of the mechanism by which this change occurs [63].

Satisfaction

Satisfaction is a subjective PRO that has intrinsic value and is central to the modern concept of patient-centered care [64] but must not be used as a surrogate for quality of recovery. Quality of recovery is a multidimensional construct that assesses the postoperative experience using both objective and subjective measures [65, 66]. While satisfaction may be assessed as a component of quality of recovery, it is a discrete entity, which is inherently solely subjective and influenced by external events, patient expectation, sociodemographic variables, and internal patient characteristics [12, 37, 64, 67]. Satisfaction as an outcome measure is hindered by its inherently subjective nature and the paucity of validated assessment tools and lack of a suitable comparator [68–71]. Satisfaction is heavily influenced by the provider-patient relationship, being improved with empathetic care, provision of individualized health information, realistic patient expectation, shared decision-making, emotional engagement, and perceived responsiveness of the patient's treating team [59, 60, 67, 68, 72–74]. It is, in, part, correlated to objective measures of recovery, with high satisfaction being associated with reduced early readmission rates [75] and low satisfaction being correlated with persistent adverse symptomatology and postoperative complications [6, 71, 76, 77]. Thus, while satisfaction has intrinsic value as an outcome in its own right, it must not be used as a surrogate for quality of care or recovery and must be measured using a validated tool assessing satisfaction in specific areas of care [68, 70].

Quantifying Recovery

Recovery fundamentally assesses a patient's postoperative performance to that of a preoperative comparator, with subsequent inference as to whether the magnitude of this difference is clinically significant. However, recovery assessment tools differ in their method by which they assess a patient's postoperative performance and, importantly, the preoperative baseline performance to which they compare.

Composite Change Scores

Recovery and its fundamental physiological processes exist along a continuum. Hence, recovery assessment begins with assigning a mathematical value to a patient's postoperative performance in a health domain of interest. These commonly take the form of Likert or visual analogue scales, where a patient's performance is assigned an integer value by either the patient or an independent observer, with 1 and 10 (or 5) being the minimum and maximum scores, respectively. Each domain is assessed using one or more health-related questions or "items." In multidimensional recovery assessment, scores from each item are then summated to produce a single postoperative score (composite score) for each patient. This score is then compared to a preoperative baseline score, with this latter score being either the patient's *own* baseline performance or, more commonly, the *average* preoperative performance of a group (either the group to which the patient belongs or a historical group). This conventional change score is referred to as a composite change score. The significance of this score can then be assessed in two ways (Fig. 35.2): either by comparison of the difference between two groups' mean change scores to determine whether different clinical pathways infer a benefit or by comparing an individual patient's change score to a predetermined threshold in order to determine whether a patient's performance is in keeping with what would be expected for "normal recov-

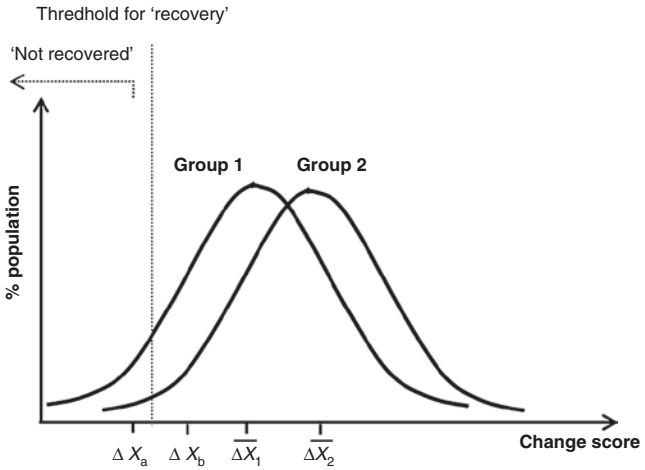

Fig. 35.2 Composite change scores. Δ(Delta)x_a, individual change score for patient a; Δ(Delta); x_b, individual change score for patient b; Δ(Delta) x_1, group 1 mean change score; Δ(Delta) x_2, group 2 mean change score

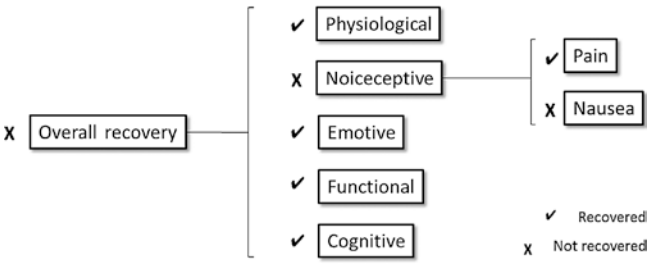

Fig. 35.3 Dichotomous recovery score. In this example, the patient has not recovered overall, due to failure to recover in the nociceptive domain due to persistent nausea (but no pain)

ery." In both assessments, a statistical significance is inferred to have clinical significance.

Assessing recovery as a composite change score is not without its limitations. Firstly, while composite scores allow for assessment of recovery in multiple domains, it assigns equal weight to each scale, which may not reflect their clinical implications; i.e., a score of 7/10 for each on the pain and nausea scales, while mathematically equal and contributing to the final composite score to the same degree, may have different clinical implications. Secondly, each domain is commonly assessed using more than one response item, but the number of response items per domain may not be equal; i.e., the nociceptive domain may be assessed using three response items, while the cognitive domain may have only one. This biases the overall composite score to reflect the domain that is assessed by the most number of response items; i.e., in the previous example, a patient with poor postoperative pain will score a worse composite score compared to a patient that may have severe cognitive dysfunction but excellent pain control. Thirdly, composite scores have the potential to "mask" poor postoperative function—demonstrable failure by a patient in one domain may be compensated for by their above-average performance in the remaining domains [78, 79]. Finally, a composite change score that is deemed to be reflective of poor recovery does not identify *in which domain* a patient's performance is suboptimal but only that is occurring.

Dichotomized Recovery Scores

An alternative method of recovery assessment is dichotomization of each domain, such that each recovery domain is assessed independently from all others. This mitigates bias due to differences in the number of items used to assess each domain, as well as that due to a patient's failure in one domain being obscured by their excellent recovery in the remaining domains. At an individual patient level, a patient is deemed to have recovered on a recovery item if their postoperative performance is equal to, or exceeds, a predetermined value (ideally their own preoperative performance). Domain recovery requires that a patient scores as "recovered" in all the items pertaining to that domain. Overall recovery mandates that a patient is deemed to have recovered in all of the domains assessed (Fig. 35.3). Group recovery is assessed by comparison of recovery prevalence rates, either overall or for each domain. Dichotomizing recovery assessment thus has direct clinical utility, as it identifies not only *in which* patients poor recovery is occurring (this patient "has recovered" vs. "has not recovered") but *in which domain*s (they have recovered in the emotive, functional domains and cognitive domains but not the nociceptive domain). This allows for targeted intervention to be given to those patients who would most benefit (physiotherapy assessment to patients with poor functional recovery and psychological review for those with poor emotive recovery). A perceived limitation of dichotomized recovery is that data richness is lost and that it identifies only the patient who has not recovered but not the magnitude by which they failed to do so. This is mitigated by recording continuous variables in their raw form, thus enabling a "drill down" of domains with poor recovery to identify its severity.

The Importance of Using the Patient's Own Baseline as the Comparator

It is essential that the comparator to which a patient's postoperative performance is assessed is the patient's *own* baseline (preoperative) performance. When ordinal scales are summated, it is assumed that there is not only mathematical equivalence *between* scales (the increments within the pain scale are identical to that on the nausea scale) but *within* each scale (i.e., the difference between 1 and 2 on the nausea scale

is the same as 9 to 10) and *between patients* (each patient assigns the same weight to each increment on the nausea scale as he or she does to the pain scale). However, as each patient differs in his or her internal cognitive framework from which he or she assesses the quality of his or her experiences, so too will he or she differ in the relative magnitude that he or she assigns to the increments *within* each scale and *between* scales. This has direct implications when a patient's postoperative performance is compared to *anything other than their own*, as in this instance the internal framework assigning value to each of the recovery scales postoperatively (the patient's) is not the same internal framework that is assigning value to the scales preoperatively (either a person other than the patient or even a group average). For example, a patient may be more likely to report a lower postoperative pain score if he or she is undergoing curative surgery compared to a patient who has undergone a palliative procedure. Similarly, a patient who has previously experienced debilitating postoperative nausea may assign a greater significance to a single increment in nausea compared to a patient who has not. In addition, by using a patient's own preoperative baseline *for each* individual perioperative event, response shift and recall bias is further reduced as it minimizes the time delay between postoperative and preoperative assessments. As each perioperative journey is assessed independent upon previous, or future, events, this minimizes the bias due to changes in a patient's internal cognitive framework as a result of chronic illness or trauma.

When assessing objective measures, comparison of a patient's postoperative performance to that *other than their own preoperative baseline* is also biased when the patient differs significantly from the reference population in regard to the recovery item being assessed. The fundamental building block of recovery assessment is comparison of a patient's postoperative performance to a preoperative reference (traditionally this being an average performance of a reference preoperative group), with subsequent assessment as to whether this difference is in keeping with what would be expected for that particular time in a patient's recovery course. A threshold difference in performance must therefore be determined, below which suboptimal recovery is deemed to be occurring. This is usually defined using common statistically significant thresholds (i.e., a change that is greater than 1 or 2 standard deviations from a reference population's average performance) that is inferred to have clinical significance.

A patient with a preoperative baseline performance significantly greater than that of the reference population is biased to be deemed to have recovered, even in the event that their postoperative function is demonstrably less than their own (high) preoperative baseline. This is as a result of the fact that the absolute value above which recovery is deemed to have occurred is based on population parameters (the average group baseline score and the accepted "normal" group variation above and below this) that may not mathematically model the individual patient's performance. A patient with high preoperative baseline is biased to be recovered irrespective of whether they experience a normal *or* demonstrable decline in postoperative function *compared to their own* preoperative baseline (Fig. 35.4). As the population-based preoperative reference is less than the patient's own baseline performance, these patients' postoperative function must decline by a larger magnitude (compared to a patient with "average" baseline function) for it to fall below the population-based threshold defining incomplete recovery. For example, a patient with high cognitive baseline may be able to recall nine out of ten words at baseline (compared to a population's whose average is six and a standard deviation of two) but only six postoperatively. If the threshold that defines poor recovery is a change score greater than -1SD from baseline, this patient would be deemed to be recovered when assessed using population parameters, but not necessarily when assessed to their own preoperative baseline. In this instance, they would be required to score less than four (a demonstrable decline from

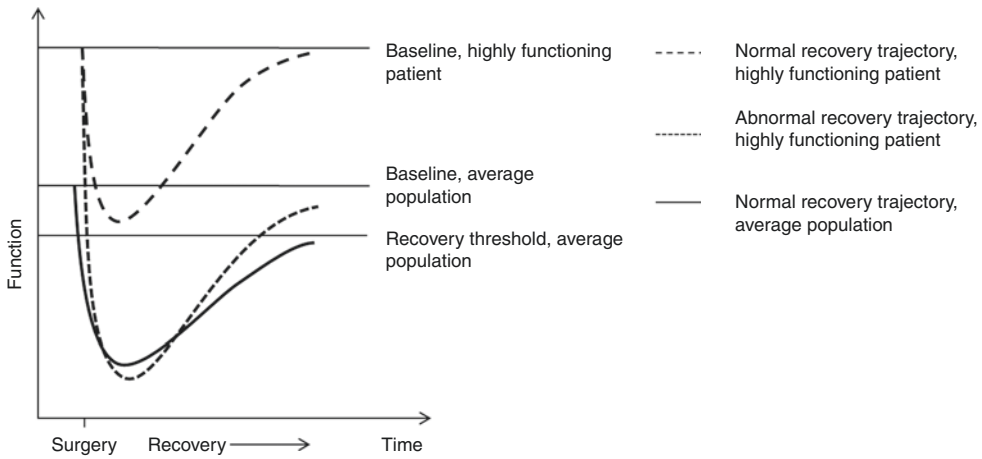

Fig. 35.4 The effect of comparing a patient's postoperative performance to their own (vs. group average) preoperative baseline

their own baseline) for them to be deemed "not recovered." It is only by using each patient as their own comparator is this measurement bias minimized.

Contextual Real-Time Recovery: The Future of Modern Recovery Assessment

Recovery assessment is complimentary to, but distinct from, traditional perioperative risk models. Perioperative risk assessments aim to predict patients in whom perioperative compilations (i.e., suboptimal recovery) may occur in order to rationalize resources to the patients who would benefit the most. Modern risk reduction tools utilize predictive analytics and patients' electronic metadata in order to drive clinical decision and improve patient outcomes [80, 81]. They are beneficial at the institutional and provider level to anticipate resource utilization. At the individual patient level, population-based risk parameters are applied to determine a risk band for each patient's perioperative event. Perioperative risk stratification does, in part, correlate with postoperative outcomes [82, 83] but requires all patients within a population (high-risk patients) to all be given a treatment in order to prevent adversity in a proportion of them and fails to address the perioperative issues (poor recovery) that may occur in a proportion of patients a priori classified as low perioperative risk. Thus, while traditional perioperative risk models predict patient *populations at risk* of suboptimal recovery (and hence resource utilization), they do not identify *individual patients in whom this actually occurs* in entirety [84].

Real-time recovery (RTR) assessment is complementary to traditional risk assessment as it identifies individual patients in whom suboptimal recovery is *actually* occurring *at the time* that it is occurring. RTR has the potential to improve patient outcome by minimizing the time delay between identification of suboptimal recovery and implementation of a corrective measure [85–92] as well as through improved patient engagement and promotion of self-efficacy [93–95].

RTR is a concept originating from information technology and organizational literature but is directly applicable to the concept of recovery as that which occurs along a time-dependent predictable trajectory. RTR is the ability of a system to detect and recover from a deviation from an expected norm in a time frame that minimizes system losses. In regard to patient recovery, RTR requires first identification of individual patients and in which domains suboptimal recovery is occurring and then implementation of a clinical corrective treatment aimed at the cause of this suboptimal recovery. RTR is thus ideally measured using a dichotomous recovery tool with contemporaneous collection and analysis of data. This real-time individualized data assessment *is in addition to*, and contrasts sharply from, traditional assessments of recovery, which have been limited to retrospective assessment of recovery between groups (rather than between individual patients).

The infrastructure and tools required for RTR assessment are already well established within the medical and surgical fields. These include data detection devices (either automated biometric technology or electronic apps collecting recovery specific parameters) and digitized analytic platforms. Automated biometric technology includes items of clothing and jewelry that provide a continuous, or high frequency, individualized biometric setting (cardiorespiratory and basic physiological variables) from which to view other measures of recovery [96]. Recovery-specific parameters range from PROMs (pain, anxiety) to procedure-specific outcomes (return of bowel function, ability to flex knee). Data is transmitted to digitized platforms either by automatic uploads through the device itself, via external hybrid devices, or by manual entry by the patient into recovery-specific smart apps. Thus, each individual patient's recovery data is assessed in context of their individual biometric profile and ideally in reference to their own preoperative baseline.

Digitized platforms are ideally tailored to the clinical context to which they are applied. For example, a recovery assessment may be tailored to include operation-specific items that a surgeon has deemed important to measure or to what has been defined by the patient as important for a successful surgical outcome. Smart devices have high population penetrance and patient familiarity [96–99], biometric technology has high patient acceptability [96], and the use of smart devices for the collection of recovery data has demonstrated proof of concept [100, 101]. Through contemporaneous collection, uploading, and analysis of data and the use of automated alerts, a clinician can be alerted at the time to a patient who is experiencing suboptimal recovery, irrespective of the geographic location of the patient (inpatient versus outpatient). In addition, by inclusion of the patient into the alert, patients are kept informed of their own recovery progress, an integral component of patient-centered care and engagement.

The Postoperative Quality of Recovery Scale (PostopQRS)

The Postoperative Quality of Recovery Scale (PostopQRS) is a dichotomous multidimensional recovery assessment tool, which has an established digitized analytic platform with real-time scoring of recovery. Recovery assessment may be tailored to the user (patient or clinician) and encompasses both basic physiological variables and the nociceptive, emotive, functional, and cognitive domains. In addition, it compares each patient's postoperative performance to their own preoperative baseline, thus minimizing measurement bias. It has both clinical and research

applications, as automated alerts can identify patients in whom suboptimal recovery is occurring at the time it is occurring (and in which domains) and retrospective assessment of data can analyze the prevalence of recovery within a clinician's patient population. It has been validated in heterogeneous patient populations, includes a cognitive domain that is based on formal neuropsychological tests and that has been calibrated for repeated assessments, and has been calibrated for assessment either face-to-face or via telephone [6, 102–104]. These attributes are essential for a tool to assess individualized patient recovery at multiple time points, both in the immediate postoperative period and post-hospital discharge.

The PostopQRS has been designed for multiple purposes, including the ability to engage patients as well as connecting them with their providers. However, other stakeholders in the health industry with interest in patient improvement can use the PostopQRS as an audit or research tool to benchmark recovery, institute health service changes, and measure the effect of interventions. This concept is illustrated in Fig. 35.5.

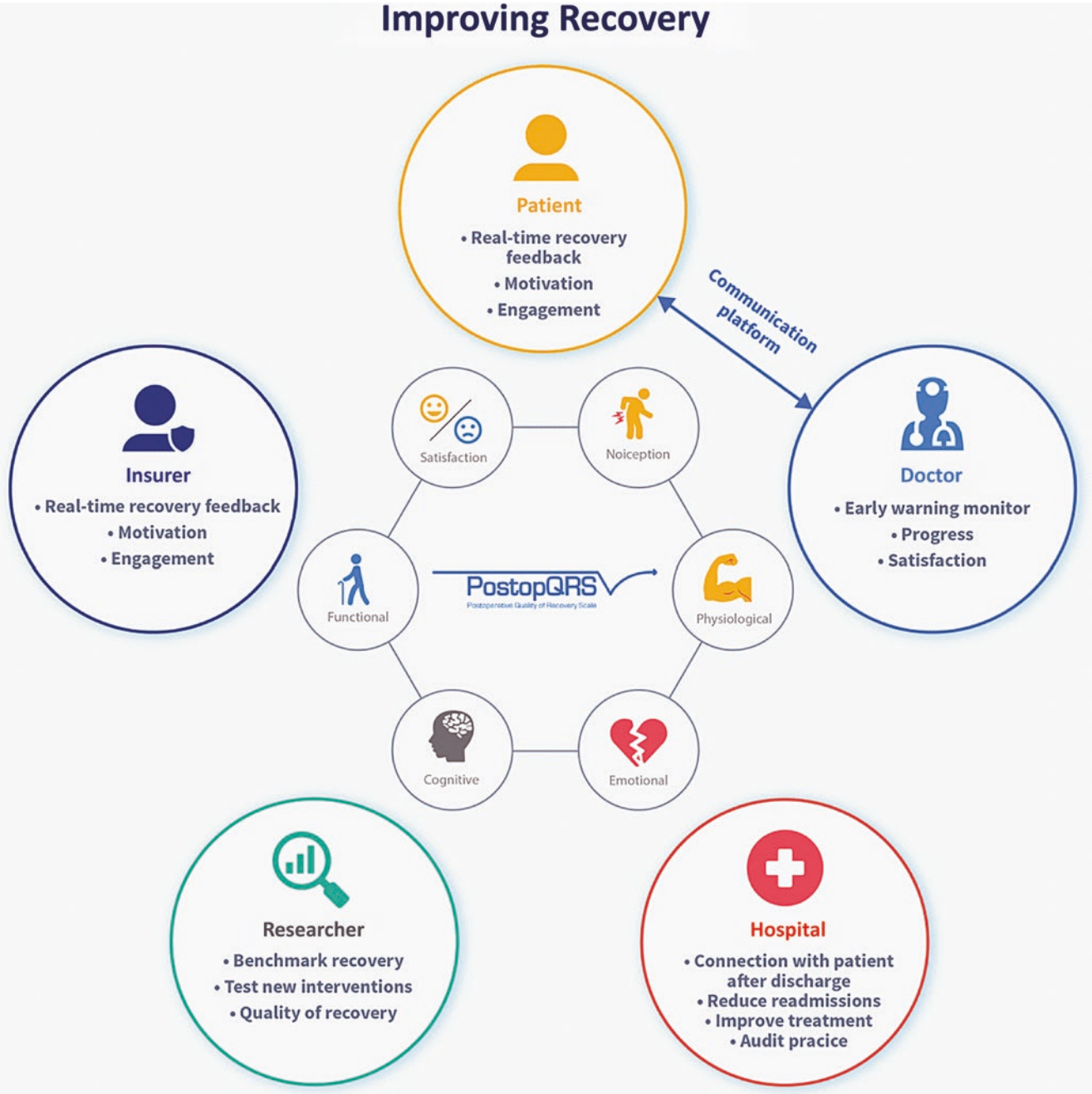

Fig. 35.5 Patient and stakeholder uses of the Postoperative Quality of Recovery Scale (PostopQRS) to enhance recovery

Conclusion

Modern recovery has progressed from a unidimensional to multidimensional construct, is defined as occurring along a predictable time trajectory, and extends beyond the traditional immediate postoperative period. The most commonly reported outcome measures used to evaluate ERAS pathways were length of stay and 30-day readmission rates. There is a call for measurement of recovery within ERAS programs to be extended beyond the use of these traditional surrogate markers of patient recovery and to include both patient-centric outcomes and contextual variables in a multidimensional assessment. Recovery assessment variables may be objective or subjective and are prone to bias due to lack of context or susceptibility to response shift, respectively. Recovery assessment infers a comparison of a patient to a preoperative comparator, ideally their own preoperative baseline. Ideally, recovery is assessed using a multidimensional dichotomous recovery assessment tool that has the infrastructure to provide recovery data to both patient and clinician in real time.

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Measuring Compliance: Audit and Data Collection

36

Julie Perinel and Mustapha Adham

Introduction

In 2005, the ERAS® Study Group published the first evidence-based care protocol for patients undergoing colonic surgery [1]. It included 20 items to reduce postoperative stress. Over the last decade, several randomized trials and meta-analyses have demonstrated the safety and the efficiency of the enhanced recovery after surgery (ERAS) program in colorectal surgery. When compared to traditional care, the ERAS program was associated with a reduction in postoperative morbidity and hospital length of stay (LOS) [2, 3]. While a number of studies have demonstrated the clinical benefits of the ERAS program, only a few studies reported the compliance. Ongoing audit of clinical outcomes is an inherent component of the care protocol and is essential to report and improve the compliance. In 2007, Maessen concluded that simply developing an evidence-based protocol is not enough to change the practice [4]. Results suggested that improving the compliance with the ERAS program was probably the most challenging area but also one that might provide the best results on the postoperative outcomes.

Successful implementation of ERAS requires the commitment of a multidisciplinary team associated to a proper and structured implementation strategy [5]. Simultaneous tools are used to measure and improve the compliance (Fig. 36.1):

- A prospective database to report the postoperative outcomes, the LOS, and the compliance with the ERAS program and each component
- Regular audit to identify the enablers and the barriers to implementation of ERAS. The ERAS® Interactive Audit System (EIAS) is based on the knowledge-to-action framework described by Graham et al. [6]. It includes identification of the problem; adaptation of knowledge to local context; assessment of barriers and enablers to knowledge use; selection, tailoring, and implementation of interventions; monitoring knowledge use; evaluating outcomes; and sustaining knowledge use.
- Frequent feedback is provided on aspects of the program that may need further improvement. The ERAS® Implementation Program (EIP) recommends weekly meetings during the initial implementation. After some time and increased experience, the frequency of the team meetings can be reduced. However, participation at the meetings remains essential for every team member [7].

There are actually different systems to perform audit and quality control. In the United Kingdom, the Enhanced Recovery Partnership Program (ERPP) was introduced by the Department of Health in conjunction with National Health Service (NHS) Improvement, the National Cancer Action Team (NCAT), and the NHS Institute for Innovation and Improvement in 2009. The implementation was performed during a 2-year program. The audit system required a prospective toolkit database, developed by the National Cancer Services Analysis Team (NATCANSAT). Data were collected via a Web-based data-entry portal. To limit missing data, ongoing data collection would benefit from a data entry mechanism [8]. The Dutch ERAS study group team working with the Dutch Institute for Healthcare Improvement (CBO) initially implemented an ERAS program using the Breakthrough series, developed by Donald Berwick in the United States. It was a 1-year implementation that required a close collaboration between the different hospitals. First, the CBO organized a site visit, and local multidisciplinary teams were formed. Then, an expert team and the CBO organized 3 monthly feedback sessions involving several centers. At these sessions, the expert team developed the barriers, and facilitators and hospitals shared their local experiences. This allowed rapid dissemination of effective implementation

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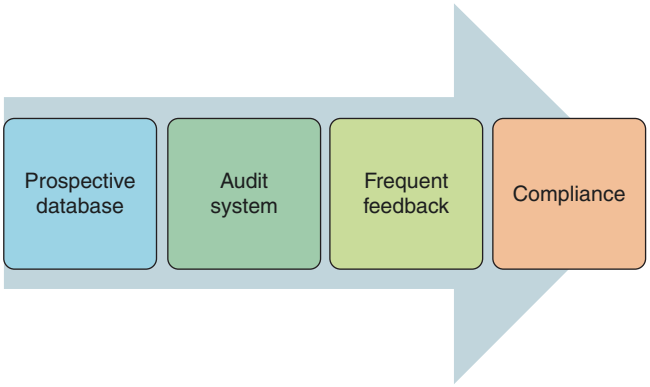

Fig. 36.1 Structured implementation strategy of ERAS program

strategies. The audit system also involved a prospective Web-based database [9]. In 2008, general surgeons in Canada developed Best Practice in General Surgery (BPIGS) with the University of Toronto to optimize patient care at adult teaching hospitals. To implement the University of Toronto ERAS guidelines, they used the knowledge-to-action (KTA) framework described by Graham et al. [6]. Reports are produced at 3 monthly intervals so each hospital can benchmark their own results against the other hospitals but also develop their own specific strategies to improve their results [10]. In 2012, the ERAS® Society group developed a specific audit system: the EIAS. It is a prospective Internet-based data entry and analysis system that monitors and measures compliance. It provides real-time feedback to centers based on all patients involved in the ERAS program (Fig. 36.2a, b). The EIP includes four seminars spread over a period of about 8–10 months. More recently, in the province of Alberta in Canada, the Alberta Health Services (AHS) started the implementation of an ERAS program in colorectal surgery. The QUERI (Quality Enhancement Research Initiative) approach was used associated with the ERAS® Interactive Audit System and the ERAS® implementation program. In addition to the strategy of Plan-Do-Study-Act cycle, the AHS includes the use of the learning collaborative, which allows the different centers to share their experiences and their performances [11]. In France, the Francophone Group for enhanced recovery after surgery (GRACE) also developed a prospective and interactive Internet-based database to obtain regular feedback on the compliance and the postoperative outcomes. Each center can also compare its results with the national ones. To date, it appears that the best system to perform a prospective and quality audit is a multicenter Web-based database with an analysis system to provide real-time feedback. The use of the knowledge-to-action framework associated with the learning collaborative is also required to reinforce practice change and to support tailored interventions. National or regional quality registries were used initially to collect data. However, with this system, feedback and comparison with other centers are not possible. Finally, "homemade" databases should be avoided due to the lack of external validation and reproducibility. Indeed, comparison between centers is limited because of heterogeneity in the data collected.

Audit and regular feedback are essential to report and to improve compliance. A Cochrane review published in 2012 aims to define the best strategy to perform effective audit and feedback. The results suggested that five feedback characteristics are required. First, feedback will be more effective if the baseline compliance is low and if the leader is a "supervisor or senior colleague." The format of the feedback is also very important. It should be delivered at least "monthly," in both "verbal and written" format. It has been shown that results are better if the conclusions are "both explicit goals and a specific action plan" [12].

Measuring compliance is essential to analyze the success of the implementation of ERAS program into daily practice. In addition, several retrospective studies have reported a relationship between the level of adherence and the postoperative outcomes [13–17]. In 2011, Ahmed et al. published the first systematic review on compliance with an enhanced recovery program in patients undergoing colorectal surgery. Despite variations in the components of the ERAS program, as well as in compliance with ERAS protocols in daily practice, high compliance was associated with shortened LOS [18]. In a large observational study of more than 900 patients undergoing colorectal surgery for cancer within an ERAS program, Gustafsson reported that a 27% increase in overall adherence to the program was associated with a 27% reduction in relative risk of morbidity and a 47% reduction in relative risk of delayed discharge. There was also a dose-response relationship between level of adherence to the program and improved surgical outcomes [15]. In patients undergoing pancreaticoduodenectomy, Braga showed a significantly higher adherence in uneventful patients, while the compliance was lower in patients with major complications [13]. More recently, a multicenter national clinical audit in the United Kingdom reported a shorter median LOS if the compliance rate is up to 80%. The authors concluded that "the more stringent the implementation of an ERAS program is, the more health benefit there will be for the patients" [8].

It is essential to understand that implementation of an ERAS program is a gradual process that requires continuous changes and ongoing involvement of the whole team. Audits are essential to identify the facilitators and the barriers to the implementation and to propose tailored intervention to sustain adherence. Retrospective audit should be favored to prevent the Hawthorne effect [9]. In a qualitative study, Lyon et al. reported four key points associated with an effective implementation and a high level of compliance [19] (Fig. 36.3):

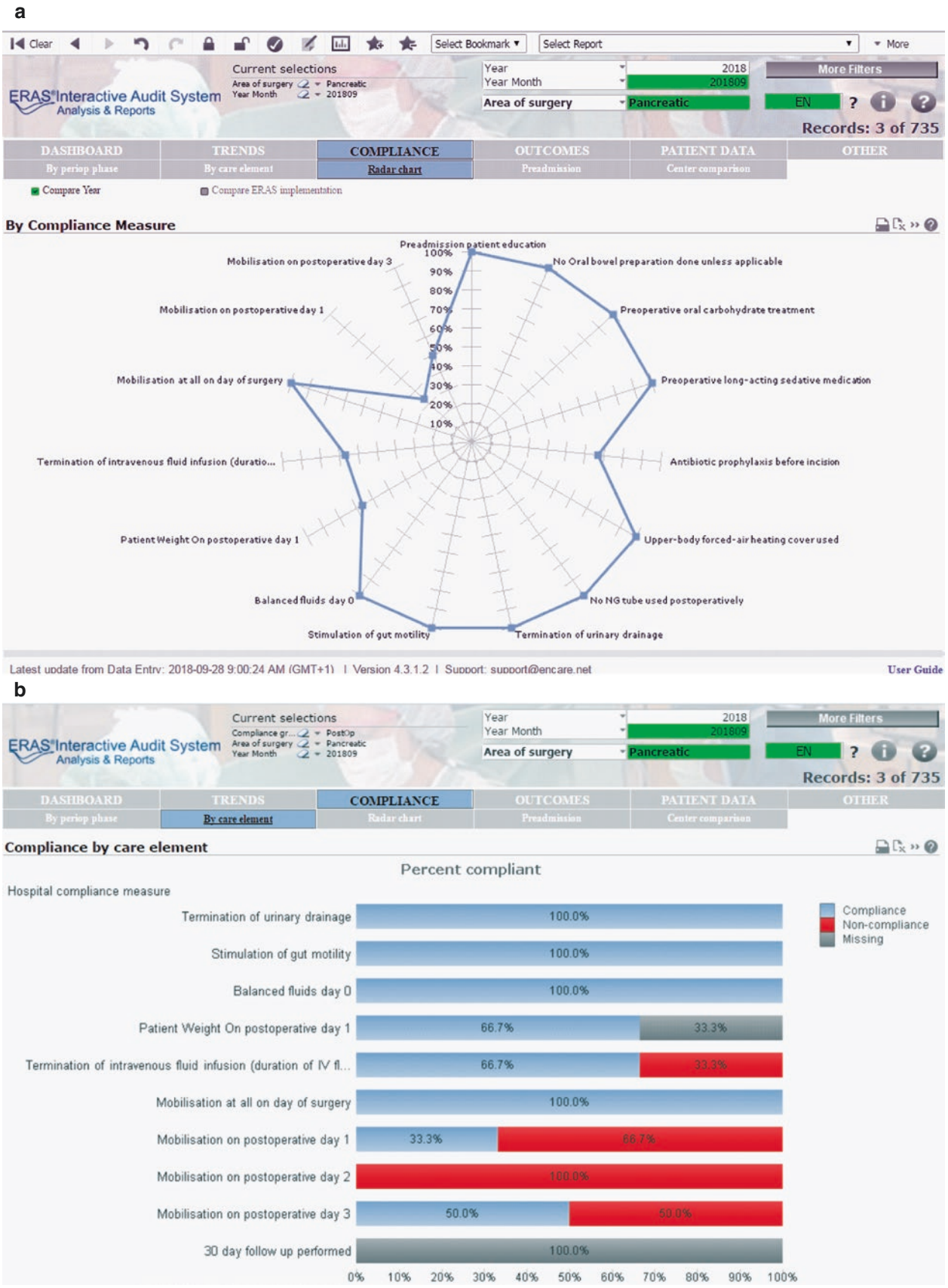

Fig. 36.2 Compliance measure with ERAS audit system in pancreatic surgery: (**a**) by compliance measure and (**b**) by care element

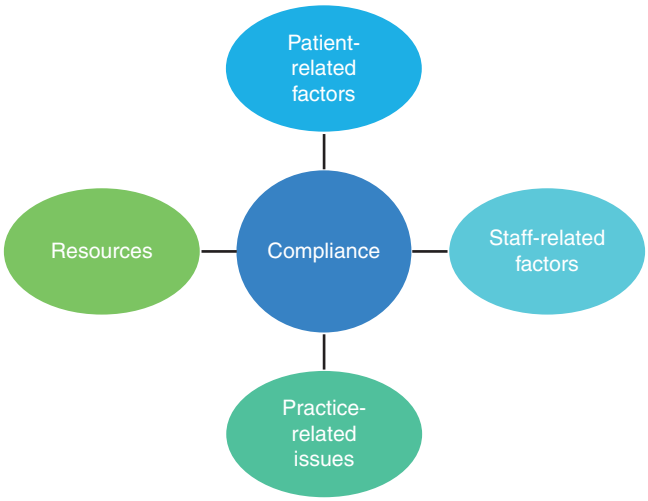

Fig. 36.3 The barriers to implementation of enhanced recovery after surgery

- The patient-related factors with patient selection (demographics, comorbidities) and patient expectation
- The staff-related factors (staff education, change of attitude, and behaviors)
- The practice-related issues (communication, standardized protocol)
- The health system resources (in-hospital and discharge resources)

From the available literature, several specific measures have been also identified to improve compliance. Firstly, education is essential. Medical staff education is required to change their behaviors and strengthen their skills. One of the main concerns lies in giving up the many years of traditional patterns and dogma. This may be facilitated by evidence-based protocols, regularly updated. In addition, regular feedback on postoperative outcomes during the team meeting will contribute to increased trust for the new program. The frequency of staff education is specifically important among doctors and nurses, because there are often changes in personnel and usually the youngest members are the main actors in the management of the patients [20]. Patients also must receive a proper and dedicated preoperative education on the perioperative pathway. Preoperative counseling with the surgeon, the nurses, and the anesthetist is one of the components of the ERAS program. Indeed, it is easier to reach a high compliance if the patient has realistic expectations of the postoperative course and the care protocol [19]. Secondly, the presence of a dedicated ERAS coordinator in each center is strongly recommended to facilitate the communication and the collaboration in the multidisciplinary team, and to improve continuity of care [17, 20, 21]. The ERAS coordinator is also responsible for the prospective database to monitor the implementation. Finally, to maintain sustainability over years, regular teaching sessions and meetings with feedback are necessary. Implementation of a new care protocol into daily routines is a dynamic and challenging process. After initial implementation, there is often a tendency to relapse into old routines [22]. Research shows that, in public health, 40% of all innovations are not sustained after initial implementation [23]. A multicentric cohort study reported a decrease in compliance associated with a trend toward longer LOS in the post-implementation period [9]. Two studies demonstrated the impact of specific measures on the compliance rate [17, 21]. In the study of Pedziwiatr, the coordinator was responsible for the prospective database and performed regular audit and analysis of the results every 30 consecutive patients. A compliance of almost 90% was reached after 2 audits and 90 patients. Some components were fully implemented from the very beginning, as they were part of standard care before ERAS implementation. On the other hand, some components were introduced gradually with a high compliance only achieved after two audits. The authors identified the following as key factors of success: close cooperation, continuous education, frequent audit, and size of the team [17]. Indeed, the introduction of the ERAS program was easier in a small department compared to large multi-profiled centers [24]. Bakker et al. reported 8 years of adherence to the ERAS program and its effect on the postoperative outcomes in colorectal surgery for cancer. After initial implementation of ERAS in 2006, the authors reported an increase and decrease in adherence. In 2011, a specialized nurse practitioner was installed. She had to call the patients within 3 days after discharge to follow up. In 2012, repeated training sessions were organized for surgical ward personnel. Case managers were introduced to attend the multidisciplinary conference on surgical indication and join the morning rounds. The patient received dedicated preoperative information about the ERAS protocol during the preoperative visit. These specific measures were associated with an improved compliance in 2012 and 2013 [21]. Martin et al. reported a 50% rate of intentional ERAS protocol deviation. In 78% of the study participants, the deviations were justified by medical reason [20]. This suggests that rather than follow a rigid program, the ERAS program should be flexible and adapted to the patient and the beliefs of the healthcare team [4, 25, 26].

While preoperative and perioperative components are often associated with a high level of compliance, the postoperative components of ERAS program are often more difficult to implement with success [4, 9, 13, 21]. Indeed, it appears that most deviation occurs in the postoperative period [27]. In pancreatic surgery, Braga reported a pre- and intraoperative compliance up to 80%. However, the postoperative compliance ranged from 38% to 66% [13]. The compliance was suboptimal for early feeding (53%), intravenous fluid withdrawal (38%), early mobilization (44%), and epidural analgesia suspension (66%). Among patients with low compliance, 71.7% had postoperative complications. This suggests that patients with low compliance in the

postoperative period should be carefully managed. In colorectal surgery, Bakker et al. demonstrated that only postoperative components of the ERAS program significantly improved the postoperative outcomes. It included no nasogastric tube, early mobilization, early oral nutrition, early removal of epidural, early removal of catheter, and nonopioid oral analgesia [21].

To improve specifically the postoperative compliance, several barriers have been identified. Nadler et al. reported the key role of the surgical residents in the postoperative management of patients undergoing elective colorectal surgery. Frequently, junior residents lack knowledge and clinical experience when compared to senior residents. As a result, they are more hesitant to allow enhanced recovery owing to uncertainty. Residents are involved in the daily clinical practice. They help the team to understand the barriers to the implementation. Staff surgeon preferences and types of surgery were major determinants of early feeding, while patient factors were major determinants of early mobilization and short LOS. Implementation of the ERAS guidelines is strongly influenced by the beliefs of the surgeon and the healthcare team. Standardization of the practice and education of the residents are essential to ensure adherence. The attending surgeon and fellow act as role models [28]. Several studies also reported a gap between functional recovery and discharge of postoperative patients [4, 9, 28]. Only 31% of patients were discharged on the day of functional recovery in the study by Maessen [4]. A multicenter qualitative study among ERAS teams reported that 29% of early discharge was judged to be difficult due to insufficient resources (home care and rehabilitation centers) [20]. This suggests the importance of administration support and financial issues. Finally, Nadler et al. identified patient and family expectations associated with the belief of the healthcare team as major determinants of early discharge [28]. Barriers related to the patients are opposing personality, comorbidities (mental illness, cardiovascular disease, and disability), family expectation, and language barriers. However, it is frequent that opposing personality and family expectation are rather the results of a lack of information. Education of the patient and his family is essential to empower the patient as an active actor of his health. It requires time and adequate communication skills. Preoperative ERAS consultation is strongly recommended and should be multidisciplinary. In addition, a patient education booklet and daily activity log were developed in the ERAS center to improve information [20].

Conclusion

Implementation of the ERAS program into daily practice is a challenging process that occurs at the level of the individual, the healthcare team, and the institution. It requires the commitment of a multidisciplinary team with good collaboration between each member, the presence of an ERAS coordinator, and continuous education. Compliance is a key element to assess the success of ERAS implementation. Additionally, there is significant correlation between the level of compliance and the postoperative outcomes. To reach a good compliance, simultaneous strategies such as regular audit, prospective database, and feedback are used. Audit is an integral part of the ERAS program and the only way to know whether there is improvement. Frequent meetings are essential to audit compliance, to identify the enablers and the barriers, to spread information, and to facilitate the communication in the team. The major concern regarding ERAS implementation is its sustainability over years. From the available literature, it appears that education and dedicated information at different levels (patient, medical staff, family) are the major keys to success.

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Success and Failure of ERAS: Prediction Models of Outcomes

37

William B. Lyman, Allyson R. Cochran, Keith Murphy, Brent D. Matthews, and Dionisios Vrochides

Introduction

An overarching theme throughout enhanced recovery after surgery (ERAS) is that the creation of standardized, evidence-based perioperative pathways leads to improved patient outcomes. Evidence of improved patient outcomes after ERAS implementation has been demonstrated throughout the literature and across a variety of surgical subspecialties. The continued success of ERAS implementation leads to an assumption that elimination of variation in patient care leads to improved patient outcomes. While this assumption may be true for many (and even the majority) of patients, some patients continue to "fail" ERAS pathways [1].

Using commonly chosen metrics to define "failure" during ERAS (increased length of hospital stay, readmission rate, morbidity), studies continue to identify many independent factors associated with "failure." Frequently, these failures of ERAS protocols are correlated with intraoperative or postoperative complications. One may wonder if complications lead to ERAS pathway noncompliance or whether the noncompliance to ERAS pathways causes preventable complications—a dilemma that will be addressed later in this chapter. As often reported in the literature, when attempting to prevent complications, one must first identify those individuals at risk for complications [2]. Risk stratification has become the cornerstone of complication prevention. More and more frequently, in order to identify individuals more prone to complications, risk stratification models (often in the form of risk calculators) are utilized [3, 4]. Employing predictive analytics and other more advanced forms of artificial intelligence (machine learning, advanced neural networks, deep learning, etc.) to optimize clinical, financial, and patient-reported outcomes has become the "Holy Grail" of the modern Clinical Precision Medicine era [5, 6].

In full disclosure, literature describing the use of predictive analytics and/or risk stratification in ERAS is sparse and to date mainly limited to the colorectal discipline [7–12]. As a result, in addition to summarizing the current literature, the following chapter represents the authors' institutional experience with ERAS implementation by the aid of advanced predictive analytics—a combination that is internally referred to as *functional* ERAS (*f*-ERAS).

Success and Failure Definitions for ERAS Pathways

The successes of ERAS implementation in a variety of subspecialties are described in great detail in other chapters of this book. An overarching observation is that ERAS has gained popularity by providing standardized, evidence-based guidelines in the areas of pain and nausea multimodal management, targeted nutrition, early mobilization, drain avoidance, pursuit of euvolemia, and utilization of structured outcomes audit [13]. The alternative to a standardized pathway is perioperative patient care based on dogma and clinical whim, leading to unnecessary variation in healthcare delivery. It has been well documented that elimination in patient care variation leads to significantly improved outcomes [14]. Therefore, it is fair to say that ERAS success is also secondary to its inherent ability to eliminate variation. However, the purpose of ERAS pathways is to eliminate *unnecessary* variation in patient care, not to eliminate variation altogether. A degree of variation is expected given the wide range of patient risk factors and clinical presentations.

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Another significant observation throughout the literature is while clinicians have noticed improved perioperative outcomes with ERAS implementation, administrators have likewise taken note of improved financial outcomes from decreased rates of complication, decreased readmission rates, decreased length of stay, and many other improved targeted metrics [15].

"Success" of an ERAS protocol is frequently tied directly to a single postoperative outcome, most commonly length of stay (early versus late discharge). Additionally, many would define "success" as an unchanged or (better yet) decreased readmission rate, decreased morbidity or mortality, and decreased healthcare expenditure. One of the more common issues encountered when comparing studies is the lack of standardized definitions for outcomes that determine the successful implementation of an ERAS protocol. Acceptable length of stay varies from institution to institution, and morbidity is often either undefined or lacks standardization of a system to standardize complications such as the Clavien-Dindo classification [16]. Hopefully, this problem will cease to exist with the widespread adoption of the Reporting on *ERAS* Compliance, Outcomes, and Elements Research (RECOvER) checklist, a joint statement by the ERAS® and ERAS® USA societies [17].

While most studies focus on the aforementioned surrogates for "success," they are by no means the only metrics to measure it. Often, the surrogate marker for "success" will vary according to the stakeholder. Clinical, financial, or patient-reported outcomes can all be markers for successful implementation of ERAS. While clinical and patient-reported outcomes should always take priority in patient care, monitoring financial outcomes (e.g., cost reduction) with an ERAS program will help to garner continued support from hospital administration and can be especially important when considering initial implementation of an ERAS program in the face of globally rising healthcare expenditure [18–22].

Another method to determine the "success" of an ERAS pathway is the overall compliance, measured as the percentage of protocol items successfully accomplished [23, 24]. Compliance is especially important for monitoring the ERAS implementation process; this percentage is very crucial, as improved outcomes are often correlated with increased protocol compliance. In many studies and at our own institution, an overall compliance of 70% generally correlates with improved outcomes [25]. In fact, 70% is a good *initial* goal. The truth is that outcomes continue to improve with increased overall compliance, and the goal for overall compliance should always be as high as possible [23, 24]. To this end, as already discussed in Chap. 36, auditing plays an integral role in both implementation and sustained "success" of an ERAS program. Auditing ensures high overall compliance, which is an excellent indicator of consistency in protocol item implementation and avoidance of complacency after initial successful ERAS implementation.

The Role of Complications on Compliance Within an ERAS Protocol

While the relationship between overall compliance and complications is often presented as a cause-and-effect relationship, in reality it is likely much more complex [23, 26]. One needs to keep in mind that complications may certainly lead to deviation from ERAS protocol items [1]. Let us consider two possible scenarios to illustrate this complex relationship:

1. Maintenance intravenous (IV) fluids are improperly continued as an oversight. Fluid overload ensues, resulting in pulmonary edema and prolonged hospitalization to wean the patient from supplemental oxygen.
2. A patient begins to show clinical signs of sepsis from an anastomotic leak. Boluses of IV fluids are administered for resuscitation given the patient's hypotension.

In both scenarios, the patient would not be compliant with discontinuation of perioperative fluids in a timely fashion. However, in the first situation lack of ERAS compliance leads to a postoperative complication, while in the second situation a postoperative complication leads to a lack of ERAS compliance. However, when major complications are excluded from analysis, increasing overall compliance is still correlated with improved clinical outcomes, denoting once again the importance of high compliance for achieving a successful implementation of an ERAS pathway [10].

Identification of Individuals at Risk for Complications

While many scoring systems have been used over the years to determine risk in medicine—e.g., Model for End-stage Liver Disease (MELD); Congestive heart failure, Hypertension, Age, Diabetes, prior Stroke-Vascular disease, Age, Sex (CHADS-VASc); Acute Physiology and Chronic Health Evaluation (APACHE); etc.—the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) risk calculator has brought postoperative risk for complications, based on preoperative demographics and risk factors, to the forefront of surgical discussion. Additional scoring systems such as the Modified Frailty Index, Portsmouth-Physiological and Operative Severity *Score* for the enUmeration of Mortality and Morbidity (P-POSSUM), and American Society of Anesthesiologists (ASA) class have been used with some success to predict which patients are at

higher risk for postoperative complications or mortality; however, none have gained the widespread acceptance of the ACS-NSQIP surgical risk calculator [27, 28]. Over the past decade, with the increased availability of data for analysis obtained from electronic medical records, and the increased computing power, new advanced statistical methods such as machine learning, deep learning, and neural networks are beginning to find a significant role in clinical medicine [29–31]. Importantly, these newer methods are not static predictive calculators. With each new data point, the statistical equations are modified in real time, leading to more accurate predictive models. As we continue to predict with increased accuracy which individuals are at risk for postoperative complications, the challenge is to identify modifiable risk factors or interventions that can decrease the rate and gravity of complications.

Predictive Analytics Within ERAS Pathways

The use of predictive analytics and risk calculators within ERAS pathways have been minimal to date and for the most part limited to the colorectal discipline. Keller et al. describe the use of the Modified Frailty Index to identify individuals at risk for prolonged length of stay. A Modified Frailty Index of 0 was strongly related to a length of stay of up to 3 days following laparoscopic surgery for colorectal cancer, while an index of 2 was strongly related to a length of stay of 14 days. Primary definition of ERAS "failure" was length of stay greater than 3 days [7, 8]. Boulind et al. described the use of POSSUM scoring to identify individuals at risk for deviation from ERAS protocol (e.g., compliance) during laparoscopic colorectal surgery. They identified pathology and intraoperative complications as independent factors to predict ERAS deviation and suggested that "failure to mobilize should be considered a red flag prompting further investigations following colorectal resection" [9]. Smart et al. used perioperative overall ERAS protocol compliance to predict ERAS "failure" after laparoscopic colorectal surgery (delayed discharge). They identified five protocol items that were associated with delayed discharge (continued IV fluids, lack of functioning epidural, inability to mobilize, nasogastric tube reinsertion, and urinary catheter reinsertion). They used these five items to create a predictive scoring system for ERAS failure and delayed discharge [10]. In another study, Lane et al. described that rising C-reactive protein (CRP) levels in the days following elective colorectal surgery within an ERAS pathway correlate with increased risk for adverse events. They suggest that a high CRP value on day 2 with a continued rise on day 3 should alert the surgeon to an increased likelihood of adverse events [32]. A recent study by Francis et al. incorporates newer methods for predictive analytics, including advanced neural networks, to predict delayed discharge and readmission following laparoscopic colorectal surgery [12]. All of these studies have a similar theme in common; they are observational in nature and for the most part recommend increased postoperative vigilance if any of these warning signs are detected in the postoperative period. Few, if any, studies recommend modification of the patient's ERAS protocol based on risk stratification.

Institutional Experience with Integrated Predictive Analytics to ERAS Pathways (*F*-ERAS)

In 2015, the leadership within the Department of Surgery at Carolinas Medical Center in Charlotte, North Carolina, identified a need to focus on outcome improvement in concert with cost optimization, given the current direction of non-sustainable growth in healthcare expenditure in the United States. Hepato-Pancreato-Biliary (HPB) Surgery was targeted as the divisions within the Department of Surgery to pilot structured treatment pathways to improve patient outcomes. With structured and evidence-based guidelines, ERAS was chosen [33]. ERAS was first implemented for pancreaticoduodenectomy in 2015 and was followed by ERAS pathways for hepatectomy and left pancreatectomy. In addition, other surgical disciplines including colorectal, urology, and head/neck surgery have followed suit with ERAS implementation.

Hurdles to initial ERAS protocol implementation and support staff "buy in" were similar to experiences described in Part IX of this book. However, a conscious decision was made to add to the complexity of the implementation by combining it with predictive analytics, since the institution already had significant application experience in this domain [34–36]. Both implementation compliance monitoring and predictive analytics for each patient enrolled to an ERAS pathway were employed. The purpose of this approach was twofold: first to ensure that implementation of ERAS was being performed in a safe and effective manner and second to provide real-time feedback on the success of ERAS to ensure continued administrative support.

For a brief background, Carolinas Medical Center is the flagship quaternary 1000-bed referral center within one of the largest healthcare systems in the United States, encompassing almost 50 acute care hospitals. The generated clinical volume in the era of the electronic medical records has led to an extremely large amount of data available for analysis. Over the past few years, the institution have used prospectively maintained REDCap™ (Research Electronic Data Capture) databases to create institutional procedure-specific risk calculators that have exceeded the predictive ability of nationally available risk calculators for our patient popula-

tion [34–36]. The risk calculators have continued to become more accurate with the addition of modern statistical techniques including machine learning and deep learning. In addition, the institution has fully utilized the ERAS® Interactive Audit System (EIAS) since 2015.

Using a combination of established prospectively maintained institutional REDCap™ databases and the EIAS, ERAS implementation was monitored for various high-risk surgical procedures (i.e., pancreaticoduodenectomy, hepatectomy, etc.), ensuring that outcomes and trends met or exceeded our historical standards while also showing cost savings. Monitoring outcomes and costs through our REDCap™ databases in combination with compliance as captured by the EIAS database showed clinicians, administrators, and support staff that implementation of ERAS was not only safe but also clinically superior and cost-efficient. This initial monitoring and proven success allowed for the planned addition of more ERAS protocols within other surgical divisions at the institution including gynecology, transplant, pediatrics, and orthopedic surgery.

Examples of Integrated Predictive Analytics to ERAS Pathways (*F*-ERAS)

The institutional predictive analytics have been integrated into the preoperative assessments of patients in order to identify high-risk individuals who may benefit from modification of patient care within a given ERAS protocol. As opposed to identifying individuals at risk and observing them more closely postoperatively, the health professionals are attempting to target carefully selected interventions or changes to our current ERAS pathway in an attempt to decrease the risk for postoperative complications (or at least identify them as soon as possible). While some of the below examples are still in their investigative phase, many have shown significant improvement in clinical, financial, or patient-reported outcomes after *f*-ERAS implementation.

A few examples of interventions targeting specific postoperative outcomes after pancreaticoduodenectomy, for which institutional predictive algorithms have been created and which include diversion from (or even an addition to) a specific ERAS pathway, are listed below:

Examples of intended diversion:

- If a high risk of urinary retention following pancreaticoduodenectomy is predicted, do not remove the urinary catheter on postoperative day 1.
- If a moderate risk of delayed gastric emptying following pancreaticoduodenectomy is predicted, do not remove the nasogastric tube on extubation.
- If a high risk of delayed gastric emptying following pancreaticoduodenectomy is predicted (including, but not limited to, patients with chronic pancreatitis or preoperative gastric outlet obstruction), an intraoperative feeding tube (typically a gastrojejunostomy tube) is placed to avoid delay in postoperative nutrition.

Examples of addition:

- If a high risk for malabsorption following pancreaticoduodenectomy is predicted, pancreatic enzymes are added to the postoperative treatment pathway.
- If a high probability of readmission following pancreaticoduodenectomy is predicted, once the patient has met discharge criteria, a modified postoperative follow-up plan is followed. Initially, patients will be contacted twice weekly using a combination of clinic and virtual visits to monitor postoperative recovery, followed by scheduled home visits for IV hydration (since almost 70% of readmissions following pancreaticoduodenectomy are for dehydration in this institution).

Examples of Addition of Items Outside the Core of a Traditional ERAS Pathway

Another intervention that targets global risk for postoperative complications is called the Clinically Meaningful Laboratory Tests initiative. Initially this program was implemented for patients undergoing pancreaticoduodenectomy and hepatectomy, and postoperative laboratory tests schedules were based on risk stratification from established institutional risk calculators for pancreaticoduodenectomy and hepatectomy. Patients deemed to be at high risk for postoperative complications received daily laboratory draws while patients at low risk for postoperative complications will receive minimal postoperative laboratories. The Clinically Meaningful Laboratory Tests initiative can be tied to the ERAS pathway compliance monitoring, to ensure high adoption rates (nearly 100%). In one institution the first year of employing the protocol saved $360,611.75 in laboratory charges alone (a 54% decrease) while maintaining clinical outcomes, increasing satisfaction, and decreasing the need for postoperative blood transfusions; the latter was not factored in the saving analysis [37].

In similar fashion to previous protocols using institutional risk calculators and maintaining high compliance rates by tying it to the institutional ERAS pathway, the ACS-NSQIP surgical risk calculator can be used to stratify patients into low-, moderate-, and high-risk categories following left pancreatectomy to guide postoperative laboratory draw schedule. While results are currently preliminary, they are quite promising in reducing patient charges by using a risk calculator that is available to all US institutions.

Prehabilitation Strategies to Augment ERAS "Success"

The body of evidence supporting prehabilitation for patients prior to undergoing major operations continues to grow. While the benefits can be implied from the perceived benefits of optimized nutrition and exercise regimens prior to surgery, benefits have not been clearly shown to date for most major abdominal operations (mainly because of the paucity of literature in the emerging field of prehabilitation) [38]. Studies within the colorectal literature have begun to show that nutritional and exercise prehabilitation alone or in combination significantly improve the speed and quality of postoperative functional recovery [39]. The addition of prehabilitation seems to be a natural addition to ERAS pathways; however, continued investigation is necessary to identify the duration, intensity, and timing of prehabilitation to benefit patients in enhanced recovery programs [40].

Given the success of prehabilitation on improved recovery following surgery in other subspecialties, prehabilitation was identified as a natural addition to ERAS pathways to augment enhanced recovery for surgical patients at our institution [41–44]. The authors are currently implementing a prehabilitation protocol for patients with HPB malignancy undergoing neoadjuvant chemotherapy before their scheduled surgical intervention (prescribed exercising, customized nutrition, anemia correction, blood glucose normalization, tobacco/EtOH cessation, psychologic support, social support, etc.). This program, termed PreOperative Learning and Readiness in Surgery (POLaRiS), is coupled with the standardized items on the ERAS pathways. Not all patients undergoing neoadjuvant chemotherapy before an HPB surgical intervention are allocated to our prehabilitation program. Enrollment is decided by utilization of institutionally derived predictive analytics to determine patients at high risk for readmission, discharge to nursing facility, and extended postoperative length of stay (Fig. 37.1). Enrolling patients in

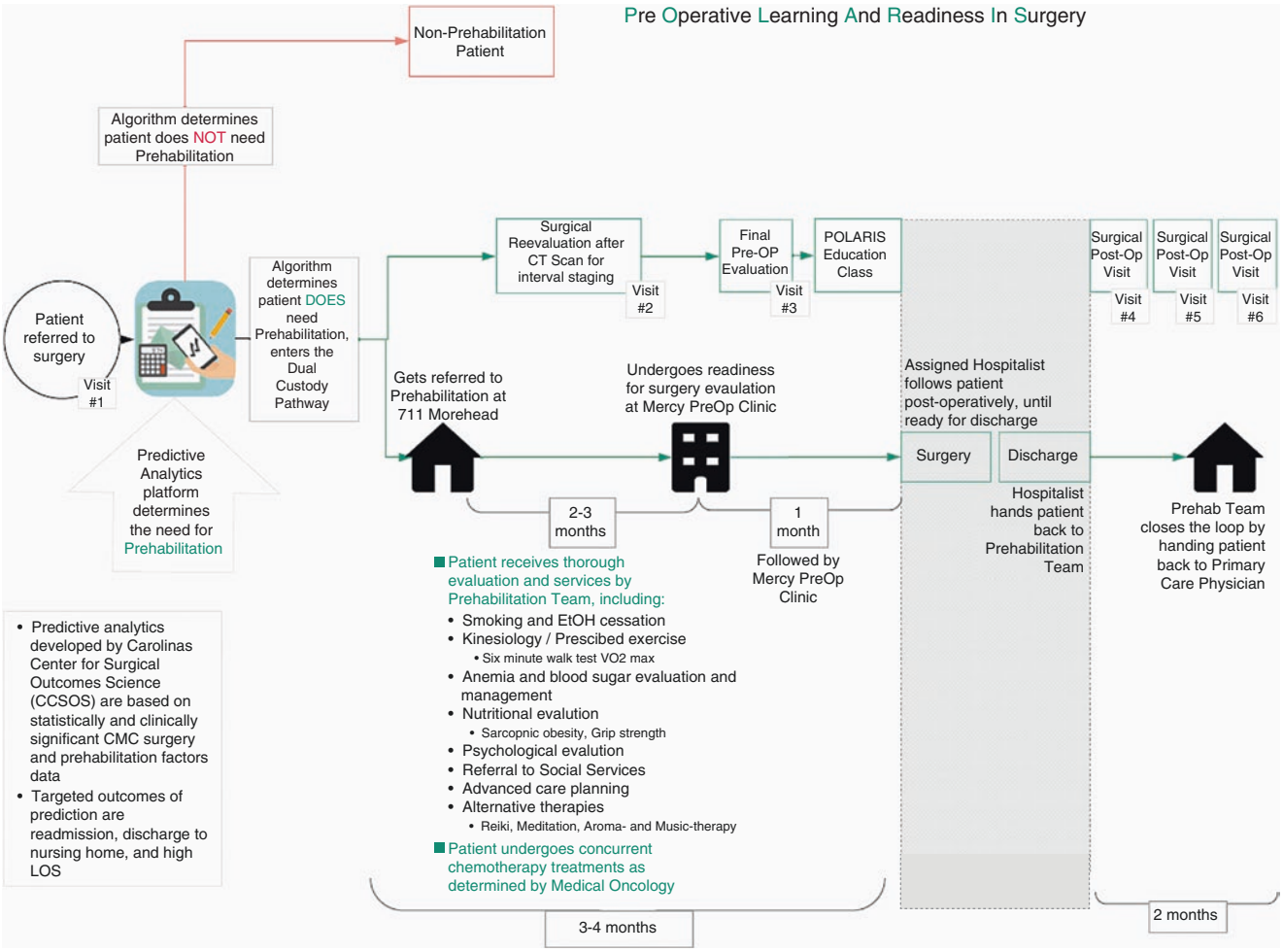

Fig. 37.1 A schematic representation of the PreOperative Learning and Readiness in Surgery (POLaRiS) prehabilitation program for patients undergoing neoadjuvant chemotherapy before surgical intervention for an HPB malignancy. POLaRiS is integrated within the HPB Surgery ERAS pathways (pancreatectomy, hepatectomy)

POLaRiS allows attempting to preemptively intervene with preoperative optimization on patients at high risk for "failure" of ERAS hopefully mitigating some of the risk for postoperative complications.

Conclusions and Future Directions

The strength of ERAS protocols is the elimination of *unnecessary* variation in patient care via the most recent evidence-based protocols. ERAS "failure" or "success" should not be defined by a single postoperative parameter but by a combination of clinical, financial, and patient-reported outcomes. Regardless of definition, many ERAS "failures" are the result of postoperative complications and not necessarily deviation from protocol or poor protocol compliance. Modern statistical methods and risk calculators are becoming more accurate in identifying patients at risk for postoperative complications, and studies are beginning to identify risk factors that contribute to complications in patients under ERAS protocols. The first challenge will be to identify modifiable protocol items and/or additional protocol items within ERAS pathways based on preoperative risk stratification. The second challenge will be to actually modify these protocol items, on a patient-to-patient basis, in order to decrease the chance for postoperative complications, and hence increase the ERAS protocol "success."

While much of the experience with ERAS and predictive analytics is institution specific, this chapter has shown some of the ways that predictive analytics and risk stratification may be incorporated into ERAS protocols. While standardization reduces unnecessary variation, a degree of variation is expected and even warranted based on the variety of patient demographics, comorbidities, and risk factors. The challenge is identifying those modifiable risk factors for preemptive intervention and possible mitigation of risk. In order for ERAS to stay on the cutting edge of medicine, there will be a need to balance the standardization of ERAS protocols with risk stratification and interventions based on modern predictive analytics and risk calculators.

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Research Methods in Enhanced Recovery After Surgery

38

Kevin M. Elias

Introduction

Research in enhanced recovery after surgery (ERAS) consists of translational studies that cover the spectrum from basic science investigations to population-based epidemiologic assessments. The term "translational science" is a broad term that encompasses both the application of laboratory findings to early phase clinical trials as well as the transition from clinical trial results to real-world practice [1]. Before embarking on any research project, an investigator should ask whether the study design has been constructed in such a way that the study results will answer the research question in an appreciable and practical way. Study design selection therefore should be commensurate with the study objectives. The goal should be to select a study design with the lowest risks of bias and confounding, but that can be feasibly done within time, cost, and ethical constraints [2]. While often conceived as a hierarchical pyramid of research, in fact, study design types are really a series of overlapping approaches that yield progressively more expansive and generalizable conclusions for patient care (Fig. 38.1).

Preclinical Research

Laboratory research is often the first step to informing changes in clinical practice. A well-designed laboratory study can answer basic questions about physiology, pathology, or pharmacologic mechanism. Useful preclinical research must be rational and testable if it is to be clinically relevant [3–5]. Increasingly, actual experiments are proceeded by in silico work, i.e., creation of computational models or simulations that can be used to make predictions and suggest hypotheses [6]. This includes "big data" science that can efficiently evaluate the biologic plausibility of hypotheses with minimal commitment of resources [7–9].

To the extent that biologic processes allow, the early stages of the discovery process still rely on in vitro and ex vivo assays. These methods provide the mechanistic rationale for studies, as these assays permit direct observation of experimental manipulation on biologic behavior, for example, gene expression, cell proliferation, or signaling pathways. In vitro assays typically refer to cell-free systems or monolayer cell culture, while ex vivo implies more complex structures, such as organ slice culture or organoids [10, 11]. Once a concept has been tested in vitro and ex vivo, ultimately its relevance to human systems requires an in vivo model. Generally, in vivo disease models can be divided into three types: (1) physiological (e.g., sepsis induced by a procedure like cecal ligation and puncture); (2) pharmacological (e.g., anesthesia via administration of sevoflurane versus etomidate); or (3) genetic (e.g., cancer formation using a transgenic mouse model) [12]. *Ultimately, however, the limitation of any laboratory model is that it is a model*. Assumptions about direct applicability to human physiology should always be tempered until clinical data exist [13].

Descriptive Studies

Descriptive studies are the starting point for clinical research. Descriptive studies include case reports, case series, cross-sectional studies, surveillance studies, and ecological correlation studies. *The characteristic feature of a descriptive study is that it presents variables without regard to a prespecified hypothesis*. While sometimes maligned for lacking scientific rigor, a good descriptive study is essential for setting precedent for future studies. A descriptive study should cover the "who, what, why, when, and where" and "so what" of a clinical condition [14]. Descriptive studies may refer to individuals (e.g., the original experience with "fast-track" surgery for open sigmoidectomy) or to populations (such as the annual

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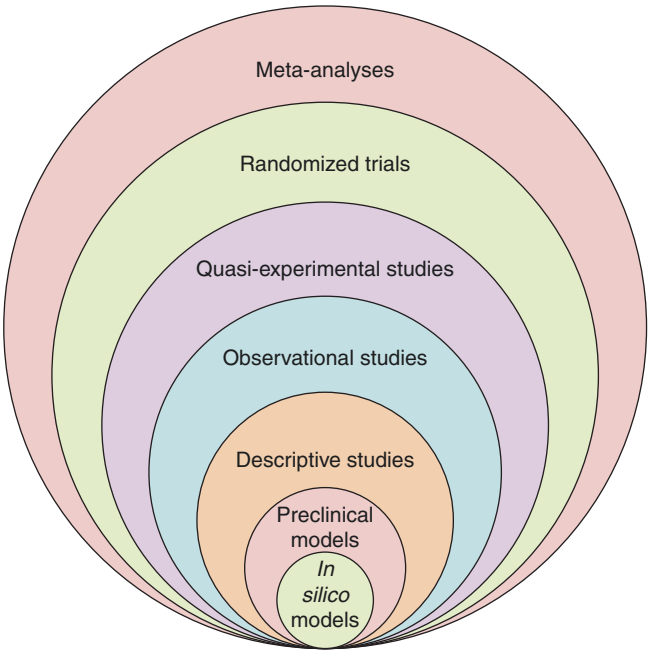

Fig. 38.1 Progression of research study designs

cancer statistics report for the United States) [15, 16]. A well-written descriptive study can uncover disease trends and suggest testable hypotheses [17].

The clear advantage of descriptive studies is that the clinical data are often readily available and easy to interpret by clinicians. However, descriptive studies also suffer from the temptation to make causal inferences [14]. Known as post hoc fallacy, descriptive reports should always emphasize that a temporal association does not mean a causal one. For example, allergists have struggled for years to dispel the myth that seafood allergies are related to the risk of iodinated radiocontrast [18]. Iodine is not an allergen, yet many hospital policies still list a seafood allergy as a contraindication to iodinated formulations. The risk factor is that a patient with atopy to any allergen is more likely to have a reaction to a second allergen; as seafood is a common allergen, many have falsely connected contrast reactions to seafood allergies.

Observational Studies

Unlike descriptive studies, observational studies test hypotheses using clinical data. The most common types of observational studies are the cohort study, the case-control study, and the cross-sectional study. The defining characteristic of observational studies is that the investigators do not intervene in any way with the study subjects, but instead relate health outcomes to underlying exposures, attitudes, or choices [19].

In the cohort study, the subjects in the study population are assigned to a group based upon exposure to a given risk factor [20]. Study subjects are then followed longitudinally through time. At the time of group allocation, the outcome of interest has not yet occurred. Cohort studies may be prospective (if enrollment occurred before the outcome was apparent) or retrospective (if data are collected once the outcome is known). Cohort studies are well suited for evaluating a series of outcomes related to a single exposure. Prospective cohort studies are particularly appropriate when the exposure is harmful (e.g., smoking) and randomization of study subjects would be unethical. Advantages of cohort studies are the ability to match study subjects based on prespecified variables and a relatively low risk of recall bias [21]. Cohort studies are useful for describing disease incidence and investigating associations between purported risk factors and health outcomes. Well-known cohort study findings include the relationship between systolic blood pressure and stroke risk in the Framingham Study and the reduced risk of ovarian cancer among women using oral contraceptives in the Nurses' Health Study [22, 23]. When assessing the strength of an association between a purported risk factor and a clinical outcome, the appropriate statistical measure is the relative risk or risk ratio (RR), i.e., the probability of an outcome in an exposed group divided by the probability of an outcome in an unexposed group [24].

Unlike a cohort study, a cross-sectional study captures all measurements at a specific moment in time rather than longitudinally. Whereas descriptive studies are useful for understanding the *incidence* of disease, cross-sectional studies are useful for understanding the *prevalence* of disease. Prevalence is the proportion of the population with a condition at a specific time point. Cross-sectional studies often use survey approaches. When cross-sectional studies are studying differences in proportions or differences in the distribution of responses to a question, $\chi(\text{chi})^2$ tests are usually appropriate. Cross-sectional studies can be performed inexpensively and quickly, but do not provide information about temporal trends [19]. For example, a cross-sectional study examined adherence to an ERAS protocol over two 3-month periods across three specialties at one center [25]. The study examined reasons for pathway deviation and correlations with patient outcomes. This captures information about a particular moment in time but does not answer whether recovery times are increasing or decreasing and cannot relate changes to the effect of a given intervention.

Case-control studies differ from cohort and cross-sectional studies because study subjects are assigned to groups when the outcome of interest is already known. The goal is to establish a relationship between the outcome and one or more possible risk factors. If cases have a significantly higher prevalence rate of a given exposure than controls, then one might conclude that the exposure is

significantly associated with an increased risk of the study outcome [21]. For case-control studies, cases and controls should be selected from the same study population. Case-control studies are most appropriate when outcomes are rare. For example, case-control studies were used to elucidate the relationship between asbestos exposure in the shipbuilding industry and mesothelioma and between extended tampon use and staphylococcal toxic shock syndrome [26, 27]. When defining cases, it is important that the case definition be as precise as possible. Explicit inclusion and exclusion criteria are needed to ensure clear demarcation between cases and controls. Unlike cohort studies, case-control studies do not allow for the direct calculation of relative risks from incidences. Instead, case-control studies produce odds ratios (OR), i.e., the ratio of disease odds given exposure status [24]. If the outcome of interest is sufficiently rare, the OR will approximate the RR, but if the outcome is frequent or the OR is particularly high, the two will be discrepant [24].

Bias in Observational Studies

Bias is any systematic tendency to encourage one outcome over others [28]. Identifying and avoiding bias is always a challenge in observational research. Some amount of bias is unavoidable, but an awareness of bias improves the likelihood that a study will yield reproducible results. Many different types of bias have been defined, but three types of bias are most prevalent in observational research: selection bias, information bias, and confounding [29, 30].

Selection bias results when the groups being studied have an underlying difference that has not been considered [31]. Examples include non-respondent bias (those not answering a survey may be fundamentally different from those answering one), incidence-prevalence bias (patients who never present to care are not accounted for in the results), and membership bias (patients choosing one health facility may be more economically advantaged than at another facility). As an example, a population-based cohort study using questionnaires to assess outcomes for ischemic heart disease patients found that clinically important prognostic variables were strongly associated with whether a potential study subject gave consent to participate in the study [32].

Information bias occurs when information has not been gathered in the same way [33]. Information bias includes ascertainment bias (cases are diagnosed by surgery, but controls are assumed to be healthy), recall bias (cases with disease are more likely to recall even trivial exposures in the past than controls, who are disease-free), and diagnostic suspicion bias (the presence of disease prompts the search for a particular exposure). In one case, results from a study linking statin use to the risk of Alzheimer disease were questioned for possible ascertainment bias since those subjects with higher statin use may have more often switched to health management organizations, possibly because they were healthier, and thus not had their claims available for review by the study investigators [34].

Confounding is the spurious association between an exposure and outcome based on a third, unmeasured variable associated with both the exposure and the outcome [35]. For example, many studies have shown that obese patients have reduced mortality compared to lean patients for specific conditions such as chronic obstructive pulmonary disease or end-stage renal disease. However, smokers tend to have lower body weights and high risks of mortality from these conditions, making smoking status an important confounder in the relationship between body mass index and health outcomes [36]. Confounding bias reduces internal validity by producing an incorrect assessment between an exposure and an outcome as well as reduces external validity by reducing the chances a finding is generalizable to another population [30].

Clinical Trials

Clinical trials are distinguished from observational studies by use of an intervention. Clinical trials may be either quasi-experimental or experimental in design. Quasi-experimental studies are non-randomized studies of interventions. Quasi-experimental studies can be important assessments of healthcare interventions when randomization is not feasible, for example, evaluating the effect of vaccines on health system outcomes [37]. While quasi-experimental studies often have more heterogeneity in the study population than randomized trials, they may be more likely to generalize to the "real-world" setting [38]. In quasi-experimental studies, investigators do not dictate the intervention assignments, whereas experimental studies imply the investigators actively intervene to produce the data, i.e., interfere with natural processes [39]. Experimental studies have the advantage of high internal validity, meaning the results are highly applicable to the exact population enrolled in the trial. However, experimental studies may suffer from less external validity when translated into real-world settings [38].

Quasi-experimental Design

Quasi-experimental studies are very common in ERAS research. Sometimes these are referred to as "natural experiments" or "self-allocation" designs. Examples include instrumental variable designs (treatment varies by an exoge-

nous variable independent of the primary outcome, e.g., a piece of equipment exists at one facility but not another), regression discontinuity designs (patients receive an intervention based on scoring above or below some threshold, e.g., CD4 count for starting antiretroviral therapy), and interrupted time series (often called "before-after" studies, e.g., facility outcomes before and after deployment of an ERAS order set) [40–42]. Many centers report their first ERAS experiences as interrupted time series with consecutive patients to describe the observed effects of introducing an ERAS pathway [43, 44].

Quasi-experimental studies can provide useful data when experimental clinical trials are not feasible. For example, randomized clinical trials presume equipoise between the treatment arms, meaning there is genuine uncertainty as to whether one treatment is better than another [45]. With many ERAS elements, randomization would be unethical. For example, when ERAS elements are considered standard of care, it would be unethical to randomize patients to only opioid-based therapies or to mandate bed rest [46]. Quasi-experimental design is also helpful when studies are done at population-wide scales. For instance, investigators looked at the outcomes pre- and post-ERAS guideline implementation for gynecologic oncology across the entire healthcare system in Alberta, Canada [47]. Finally, quasi-experimental designs are useful when political or practical considerations hinder dictation of the intervention. A study of opioid prescribing patterns showed that ERAS interventions focused on anesthesiologists led to an increase in opioid-free anesthesia and multimodal analgesia but did not impact subsequent surgeon prescribing practices for opioids on discharge, as the anesthesiologists did not have a means to mandate the surgeons' behaviors [48].

Experimental Clinical Trials

Experimental clinical trials can be divided into explanatory trials and pragmatic trials (Fig. 38.2). Explanatory trials focus on efficacy. In a controlled situation, does an intervention produce a beneficial effect under optimum conditions? In contrast, pragmatic trials measure effectiveness. What is the benefit associated with use of an intervention under "real-world" conditions [49]? *While the paragon for clinical trials is often felt to be the randomized controlled trial (RCT), in practice, explanatory trials like RCTs are not always the most appropriate or even most desirable study design.*

During a randomized controlled trial, willing study subjects with a particular medical condition and meeting narrow eligibility criteria are randomly assigned to one or more experimental interventions or a control group. The control group may consist of a placebo medication or sham procedure or simply be the current clinical standard of care. The

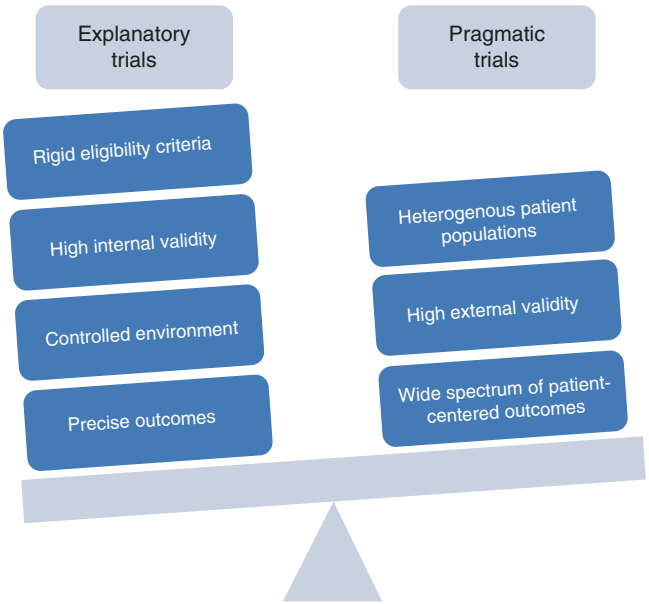

Fig. 38.2 Differences between explanatory and pragmatic clinical trials

essential element of the RCT is that the participants are assigned to an intervention by chance, thus minimizing the opportunities for bias [50, 51]. Several features distinguish an RCT from a pragmatic trial [52]. First, are the inclusion and exclusion criteria narrow and well defined [53]? If the eligibility criteria are nebulous, the study is likely to lack internal validity. Second, is the allocation scheme well explained? "Allocation" refers to the means of generating the random group assignments [54]. Third, were adequate efforts made to conceal the allocation? "Concealment" describes the process of not revealing the assignments until the intervention [55]. This includes both concealing the actual assignments but also the allocation scheme. For example, if patients are known to be allocated to study groups in random blocks of 4, then one could guess the next group assignment based on the prior 3 study participants. Both allocation and concealment work against selection and confounding bias. Finally, what procedures were taken for blinding? "Blinding" is knowledge of the treatment assignments after the intervention [56]. Blinding reduces reporting bias and ascertainment bias [57]. Trials are often referred to as single-blinded (study subjects do not know the group assignments), double-blinded (neither study subjects nor investigators know the assignments), or triple-blinded (study subjects, investigators, and data analysts are all unaware of the assignments). In practice, these terms should not be used in reporting a study; rather it is better to simply state which personnel were aware of the group assignments.

The same principles that make RCTs rigorous (controlled environment, precise inclusion and exclusion criteria, blinding) can simultaneously limit generalizability [58]. The

tightly regulated conditions of a clinical trial might have limited external validity to actual clinical practice. Whereas explanatory trials like RCTs are useful for testing "if and how an intervention works," pragmatic trials test "whether an intervention actually works in real life" [59].

Pragmatic trials are useful when the question is not one of elucidating biologic mechanism or plausibility but of establishing whether innovations have the potential to improve daily medical practice. Explanatory trials tend to focus on one specific patient population with one problem. Excluding complex study subjects (e.g., patients with comorbid conditions or taking multiple medications) minimizes confounding. For testing a biologic theory this is important. However, these conditions do not mimic clinical practice. Pragmatic trials frequently involve complex interventions with multiple interacting components, such as bundles, pathways, or protocols [60]. Patients in the trial are reasoned to be similar to patients who would normally receive the study intervention under usual care conditions. The eligibility criteria are typically less stringent, and the study outcomes tend to be broader and less physiologic in nature. Given the multidisciplinary, multispecialty, and multidimensional nature of ERAS, many research questions are better suited to pragmatic trials than to the strict limits of the RCT.

Study Outcomes

Study outcomes are dependent variables that are hypothesized to be causally related to the independent variables under investigation. For example, if the independent variable is use of an intravenous propofol infusion during spinal fusion surgery, then the primary outcome could be the incidence of postoperative nausea and vomiting within 24 h of extubation. The hypothesis would be that propofol infusions intraoperatively reduce postoperative nausea. As noted previously, however, most ERAS studies will provide evidence of associations, not explanatory mechanism. Even so, when selecting outcomes, one should still aim to identify measures that can be plausibly linked to the variable being studied.

Outcomes are designated as primary or secondary. The primary and key secondary outcomes must be prespecified in the study design prior to commencing the study. There are two principal reasons for this. First, a clear primary outcome provides a rational basis for the power calculation [61]. Plainly, power is the likelihood that the sample size is large enough to reveal true effects. A properly powered study minimizes the chances of a false-negative (Type II) error, i.e., rejecting a true association when one truly exists. Second, limiting the number of secondary outcomes reduces the risk of false-positive (Type I) errors [62]. The likelihood of identifying spurious associations by random chance alone increases in proportion to the number of outcomes being measured; this is often referred to as the multiple testing problem. While the threshold for statistical significance can be adjusted to account for the number of variables being tested, a better study design is to focus the study on the most important secondary outcomes [63, 64].

A common strategy to assess multiple end points without losing statistical power is to use composite outcomes. Composite outcomes aim to improve statistical efficiency by combining several outcome measures (e.g., mortality, serious morbidity, and readmission) into one end point. This is particularly useful when the total incidence of a given event, say mortality, is rare in the study population. However, caution should be used when implying that the results of a study apply to the individual components of the composite rather than to the overall composite measure, especially if the associations for the individual components do not trend in the same direction [65].

The primary outcome is assumed to be of more clinical significance than the secondary outcomes. Designation of outcomes as primary or secondary implies a hierarchical ranking of importance by the study investigator [66]. For ERAS studies, the primary outcome should always incorporate the concept of the minimal clinically important difference (MCID) [67]. MCID is the smallest unit of substantive benefit to the patient [68]. This is particularly important when assessing studies using patient-reported outcomes such as visual analog scales (VAS) or Likert scales. Given a sufficient sample size, statistically significant differences of fractions of a scale unit may be found, but these are not likely to impact clinical practice. In a well-known example, investigators performed a randomized clinical trial of acupuncture versus sham procedures for knee pain. The primary outcome was average knee pain on a 0–10 scale. While statistically significant differences were found between the acupuncture group and the sham procedure group, the between-group difference did not reach the authors' prespecified threshold for MCID of 1.8 units on the pain scale [69]. Thus, the authors appropriately concluded that acupuncture did not offer a clinically significant benefit, at least within the power limitations of the study.

The relevant outcomes for ERAS research vary among stakeholders, e.g., payors, patients, and physicians. However, one overarching principle is that study outcomes should be selected with the goal of making a study comparable to the existing literature. Excessive variability in definitions and measurements precludes comparisons of outcomes across studies [70]. The COMET (Core Outcome Measures in Effectiveness Trials) initiative aims to define core outcome sets (COS) that should be measured and reported in all studies pertaining to a specific clinical area [71]. These core outcomes do not imply that a study needs to be restricted to

just those in the set, but it ensures that the findings of a study will be useful for meta-analyses and informative for future clinical trials. Outcome measures should also be distinguished from process measures. Process measures determine if the protocol is being followed; outcome measures examine whether the protocol is having the desired effect.

Study outcomes for ERAS research can be broadly classified into four domains (Table 38.1, [72–81]):

1. *Administrative outcomes relate objective hospital data*. Common examples include length of stay, total direct cost, readmission rates, and opioid prescribing patterns [72–74]. Administrative data are useful for doing cost analyses and return on investment calculations, but do not directly inform whether an intervention is clinically beneficial to patients.
2. *Clinical outcomes are based on the provider's assessment* of the patient. Presence or absence of disease, survival or death, ostomy function, and the incidence of complications are clinical outcomes [75, 76].
3. In contrast, *patient-reported outcomes relate the patient's experience* [77–79]. The ability to eat or drink without nausea, quality of life surveys, and health attitude screens are all patient-reported outcomes. Patient-reported outcomes may be subjective (such as rating symptoms on a scale) or objective (such as the presence of absence of vomiting).
4. Finally, *functional outcomes are objective assessments of the ability to perform specific tasks*. The ability to ambulate without assistance, shower independently, drive, and return to work are all functional outcomes [80, 81].

As ERAS protocols have matured and more clinical data exists, functional and patient-reported outcomes are increasing in prominence as primary outcomes for studies rather than administrative or clinical outcomes. This stems from an increased emphasis on patient-centered care and a recognition that patients may perceive priorities differently in selecting among therapeutic options [82, 83].

Table 38.1 Domains for study outcomes

Type	Definition	Example	ERAS references
Administrative	Objective hospital data	Length of stay, cost	[72–74]
Clinical	Provider assessment of patient	Wound infection, fluid overload	[75, 76]
Patient reported	Patient assessment of symptoms	Anxiety, nausea, quality of life	[77–79]
Functional	Ability to perform specific tasks	Shower unassisted, drive	[80, 81]

Reporting ERAS Research

The formatting of ERAS research reports is a key element in ensuring the data are contextualized, interpretable, and reproducible. A complete ERAS report should clearly describe the implementation and use of the various elements of enhanced recovery. Accurate reporting includes a complete listing of the treatment protocol as well as the compliance with various elements as measured through audit. Unfortunately, many ERAS reports have historically omitted sufficient information for subsequent groups of researchers to faithfully reproduce the results. A review of 50 ERAS studies by Day et al. found that fewer than half of studies mentioned all the basic concepts of enhanced recovery, fewer than a quarter defined or explained the concepts, and fewer than 10% presented data on ERAS compliance [84]. Insufficient detail in reporting impedes the subsequent production of meta-analyses and systematic reviews. Across various areas of biomedical research, a systematic review of meta-analyses found that more than 80% of studies do not conform to published reporting guidelines [85]. This increases the chances that systematic reviews and meta-analyses will find data insufficient or reach equivocal conclusions [86, 87].

For this reason, the ERAS® Society and ERAS® USA published a joint statement on reporting guidelines for ERAS research known as the Reporting on ERAS Compliance, Outcomes, and Elements Research (RECOvER) checklist [88]. Study design and reporting standards have been found to improve the usability of research results [89]. The RECOvER checklist is not proscriptive, but the societies recommend using the tool to guide design, implementation, and reporting of ERAS-related research. The checklist has 20 elements and should be submitted as a supplement to ERAS reports (Table 38.2, [88]). The most detailed element is item 11, which summarizes 16 basic concepts of enhanced recovery that should be addressed in any ERAS protocol.

Conclusion

ERAS research is rapidly expanding and changing surgical practice. ERAS is rooted in evidence-based medicine; therefore, the success of ERAS pathways will be dependent on the production of high-quality research. As most surgical disciplines adopt ERAS principles, there will be a growing need to reassess old surgical paradigms within the context of ERAS-based care. These studies should be constructed with careful attention to design, outcome selection, and reporting formats to maximize the utility of these results.

Table 38.2 The RECOVeR checklist for reporting of enhanced recovery research [88]

Item		Recommendation	Page
Title			
Title	1	Indicate that this is an enhanced recovery study in the title	
Introduction			
Background	2	Explain the area of uncertainty that the study seeks to address	
Guidelines	3	If a published set of enhanced recovery guidelines exists for this procedure, include a reference to the guidelines	
Outcomes	4	Define the primary outcome and any key prespecified secondary outcomes for the study	
Methods			
IRB approval	5	Give the Institutional Review Board/Ethics Committee name and approval number. If permission was not required, reasons should be stated	
Study design	6	Indicate what type of study is presented (randomized controlled trial, cohort, cross-sectional, etc.). The individual guidelines for the type of study should be followed (e.g., CONSORT for randomized controlled trial, STROBE for cohort studies, etc.)	
Setting	7	Describe whether this is a single or multicenter study, the type of practice (academic vs. community, tertiary vs. primary), and the providers (limited group or all providers on a service)	
Timing	8	Describe periods of recruitment, time points at which outcomes assessed, and follow-up	
Participants	9	Define study inclusion and exclusion criteria	
Enhanced recovery protocol	10	Describe when the enhanced recovery protocol was implemented relative to the study period	
	11	Provide a flow diagram or table through the continuum of care detailing the enhanced recovery protocol including the following elements:	
		(a) Preadmission patient education regarding the protocol	
		(b) Preadmission screening and optimization as indicated for nutritional deficiency, frailty, anemia, HbA1c, tobacco cessation, and ethanol use	
		(c) Fasting and carbohydrate loading guidelines	
		(d) Pre-emptive analgesia (dose, route, timing)	
		(e) Anti-emetic prophylaxis (dose, route, timing)	
		(f) Intraoperative fluid management strategy	
		(g) Types, doses, and routes of anesthetics administered	
		(h) Patient warming strategy	
		(i) Management of postoperative fluids	
		(j) Postoperative analgesia and anti-emetic plans	
		(k) Plan for opioid minimization	
		(l) Drain and line management	
		(m) Early mobilization strategy	
		(n) Postoperative diet and bowel regimen management	
		(o) Criteria for discharge	
		(p) Tracking of post-discharge outcomes	
Enhanced recovery auditing	12	Describe the audit system for compliance with the enhanced recovery protocol and how compliance data are measured	
Outcomes	13	(a) Explain the criteria for assessing primary and secondary outcomes	
		(b) Distinguish among clinical, functional, administrative, and quality of life outcome measures	
PROs	14	If patient questionnaires are used, provide references to validation of these study instruments.	
Results			
Patient population	15	Use a flow diagram to explain the derivation of the study population	
		(a) Provide a Table I with the key demographic and clinical features of the study population	
		(b) Indicate number of participants with missing data for each variable of interest	
Enhanced recovery compliance	16	Provide a Table II with average compliance for each enhanced recovery protocol element and present a comparison of the variation in enhanced recovery compliance among the study groups	
Correlations	17	Perform logistic regression to correlate the change in primary outcome with the study intervention	
Discussion			
Context	18	Explain what the study adds to the body of knowledge regarding the study intervention within the context of enhanced recovery after surgery care	
Limitations	19	Discuss the limitations of the study and how these might temper the findings	
Other information			
Funding	20	Document all sources of funding and potential conflicts of interest for the study authors	

IRB institutional review board, *CONSORT* Consolidated Standards of Reporting Trials, *STROBE* STrengthening the Reporting of OBservational studies in Epidemiology, *PROs* patient-reported outcomes

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Toward a Learning System for ERAS: Embedding Implementation and Learning Evaluation

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"The success of organizations depends on their ability to design themselves social learning systems."
– Etienne Wenger

Introduction

Contemporary colorectal surgery was often associated with long length of stay (8 days for open surgery and 5 days for laparoscopic surgery), high cost, and rates of surgical site infection approaching 20–30%. During the hospital stay for elective colorectal surgery, the incidence of perioperative nausea and vomiting (PONV) may be as high as 80% in patients with certain risk factors. After discharge from colorectal surgery, readmission rates have been noted in past to be as high as 35.4%.

The concept of a multimodal approach to recovery after surgery was initially proposed by Kehlet who explored the possible determinants of postoperative morbidity in the late 1990s [1]. He identified potential risk factors that need to be recognized and treated perioperatively to minimize the effects of surgical stress on the patient. Kehlet also championed the idea of working within an integrated multidisciplinary framework. Together these efforts have led to a series of interventions that are formulated into standardized protocols to span a patient's entire journey through the surgical process with distinct elements in the preoperative, intraoperative, and postoperative phases [2].

The outcomes of interest to patients and providers include freedom from nausea, freedom from pain at rest, early return of bowel function, improved wound healing, and early hospital discharge. The basic premise is that the impact of surgery on the metabolic and endocrine response systems are reduced, leading to earlier recovery. Successful implementation of ERAS leads to reduced length of hospital stay and earlier return to productivity. Systematic reviews of ERAS for various types of surgery have shown that the intervention has the potential to enhance patient outcomes but that consistent implementation is required [3, 4]. In this chapter, we describe how the concepts drawn from the field of implementation science can be used to improve the consistency and quality of ERAS implementation while engaging front line clinical staff [5, 6].

Management of Surgical Risk and Quality Improvement

It is widely understood today that the first step toward implementing ERAS to assure patient safety and quality of care is to address several factors that are external to the surgical process itself. Scaling up in new hospitals and countries requires attention to much more than the surgerical interventions and requires an appreciation for introducing standardized processes in complex systems and appreciation of the implementation contexts [7]. These steps involve (1) developing a standard set of activities that are needed to deliver ERAS within a health system (over and above the clinical steps themselves); (2) identifying the operational factors (e.g., political will, resources, schedules, supplies, equipment, etc.) that affect the implementation of ERAS within the system; (3) identifying the organizational factors (e.g., staff motivation, organizational culture, climate for innovation) that affect the implementation of ERAS; and (4) developing a tailored, locally appropriate and bottom-up strategies to address the organizational and operational factors based on local constraints and championship. In essence, effective hazard reduction and risk management requires a reframing of care from one that is task-oriented at the level of the

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practitioner to a systems-based, patient-centered one that looks to the actual relationships within the socio-technical surgical microsystems and the operational and organizational characteristics of the meso- (and possibly macro-) system in which care is conceived and delivered [8–10].

At the most basic, this involves a reconceptualization of the patient from the passive object of medical intervention to an active "consumer" or "user" of health services who *coproduces and* "*owns*" *their own health* [11]. The risks and hazards of health care are known frequently to be the result of ineffective systems design rather than poor performance by surgeons and other individual providers. Preventable errors occur in health care because of the interaction between "latent" organizational system failures and "active" errors by frontline actors, possibly in ignoring or responding inappropriately to system failures [12]. Multiple latent conditions, or "organizational pathogens," may be designed into the processes and structures of care, thereby increasing the likelihood/risk of failure/error at the patient-provider interface, sometimes because of unforeseen interactions between pathogens.

An Organizing Principle for ERAS Implementation: The Modified Donabedian Model

The Donabedian model is a well-known conceptual model developed in 1966 to examine factors affecting the quality of health care delivery [13]. The model describes the health system as comprising three major linked components: structure, process, and outcomes. *Structure* refers to the settings where care is delivered and encompasses the physical and organizational characteristics of the care delivery environment. *Process* incorporates not only the clinical activities performed by physicians and other care providers but also all the other aspects of delivery that affect the overall patient experience within the health system, such as short wait times, transparent and clear communications, dignity and respect for patient and family, or compassionate care. Finally, *outcome* encompasses not only the results of the surgical procedure but also the other quality domains identified by the US Institute of Medicine, such as patient centeredness, timeliness, reliability, equity, or efficiency [14].

We will use an expanded version of the Donabedian model as the organizing principle for this chapter [15]. The version, shown in Fig. 39.1, expands the process stage of the model to illustrate that the range of interventions needed to achieve outcomes extends beyond surgery and even beyond the interventions linked to the preparation for the surgical procedure into generic health system-strengthening interventions such as leadership development, technology infrastructure development, communications training, or, in low-resource settings, even foundational components of the setting such as staff hiring and retention, supply chain management, or equipment maintenance. The field of implementation science, which we present later in this chapter, focuses on how we learn as a system and defines the clinical and service interventions as "intervention-specific capacities" and the generic interventions as "general capacities" [16]. Both sets of capacities are needed for the successful, reliable, and sustained delivery of any clinical intervention, and these are particularly critical for multicomponent interventions such as ERAS that are a mix of medical, organizational, and behavioral interventions. The success of ERAS is based not only on how well the surgeon and anesthesiologist and other surgical team members perform but also on clear actionable information provided to patients on perioperative care, criteria for discharge, how to address post-discharge complications, and follow-up protocols [17].

Each of these components of the intervention needs to be alinged for effective ERAS outcomes such as reducing readmission rates, which means that in addition to the surgeon's skill, there is the need for effective communication, gaining the patients' trust, facilitating post-discharge compliance, assuring that the community is ready to receive the patient, and other processes that make up the targeted and generic service intervention components [18]. But while these components may be obvious in theory, the fact still remains that they are challenging to implement in practice [19]. Processes need to be designed, and interventions need to be implemented and

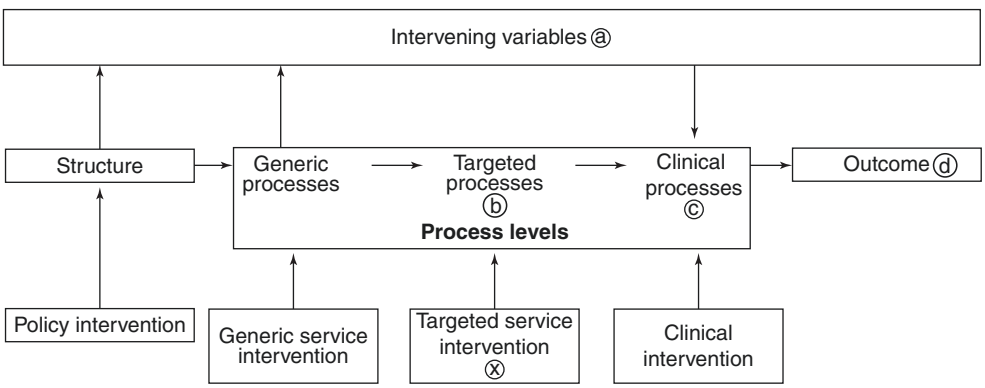

Fig. 39.1 Modified Donabedian causal chain. Interventions at structural (policy) and generic service level can achieve effects through intervening variables (such as motivation and staff-patient contact time) further down the chain. For example, an intervention at (x) produces effects (good or bad) downstream at (a), (b), (c), and (d)

adapted to fit the local context, which is highly shaped by the local culture and context, while still remaining true to the basic principles of ERAS [20]. We will use an implementation framework to operationalize the expanded Donabedian model.

The Design Focused Implementation Framework

Implementation scientists have developed more than a hundred frameworks to guide, assess, sustain, and improve the implementation process [21]. As yet, there is no standard methodology for framework selection, and implementation scientists use their expertise and judgment to select the best framework to suit the unique clinical or organizational needs. In this chapter, we select a framework that is best suited for implementing interventions de novo, where key delivery system processes do not exist and need to be designed from the ground up, such as when hospitals are planning to start implementing an ERAS program (Fig. 39.2) [22].

The framework consists of three components: design, implementation, and evaluation. The design component relies on the principles of experience-based co-design (EBCD) to develop delivery processes that best meet the needs of the patients and their families [23]. The implementation component identifies context-specific barriers and facilitators to implementation and develops strategies to overcome these barriers based on deep, local knowledge. The improvement component monitors both the process of implementation and the routine system performance post-implementation and uses this performance data to make necessary course changes to the system. The three components are linked together through a comprehensive mixed-methods process evaluation.

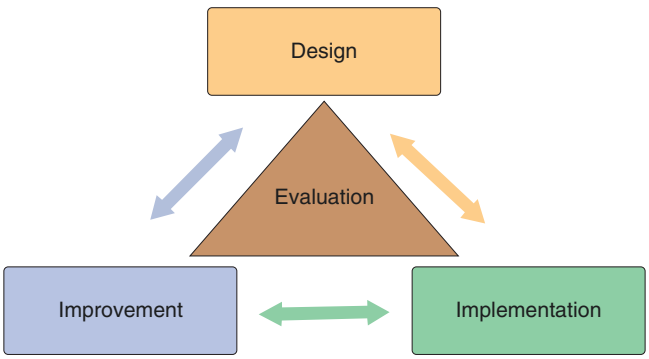

Fig. 39.2 Design Focused Implementation Framework (DFIF)

Designing the System: The Experience-Based Co-design Approach

Let us consider how this framework can be applied to create a comprehensive system for ERAS implementation. The first step is to create a set of standard clinical and organizational processes for the entire surgical experience. These processes could include pre-surgery consultation, orientation packages, communication prior to the surgery date, check- in processes on the day of surgery, patient mapping, discharge protocols, post-discharge communication, and follow-up in addition to the activities of the ERAS clinical intervention itself. The process mapping is designed with the needs of the patient, and their caregivers, in mind and is oriented to optimize the patients' experience during their interaction with the health system [24]. EBCD is a structured process that couples a detailed analysis of the facility workflow with video interviews of patients' to create "trigger films" for discussion. Patients and staff view the trigger films together to identify opportunities to improve the patients' experience and then charter small co-design, clinician led groups to address priority issues that arise [25]. The EBCD framework transforms and elevates the role of the patient to a true co-creator of the design process and services. Figure 39.3 shows the continuum of roles that a patient can play in interactions with the health system [23]. As we move from left to right in the figure, the power differential between the health system and the patient diminishes, a as the patient is actively involved in the co-production of the experience.

Implementing the Design: The Role of Implementation Research

The outcome of the design process is the set of processes, protocols, organizations, physical structure, materials, etc. that wrap around the clinical intervention to facilitate and support its success. But a good design alone is inadequate unless it is implemented well [5]. The emerging field of implementation science is dedicated to the study of local and organizational factors that affect the success of implementation and to develop and test context-appropriate implementation strategies that can enhance the acceptability and adoption of an innovation within an organization [6]. The design of the ERAS system can be more effectively implemented using the frameworks and tools of implementation science. One of the most commonly used frameworks is the Consolidated Framework

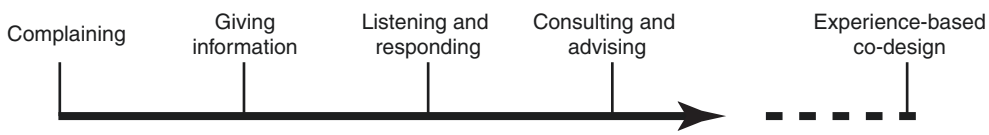

Fig. 39.3 The continuum of co-design roles of the patient. (Reprinted with permission from Bate and Robert [23])

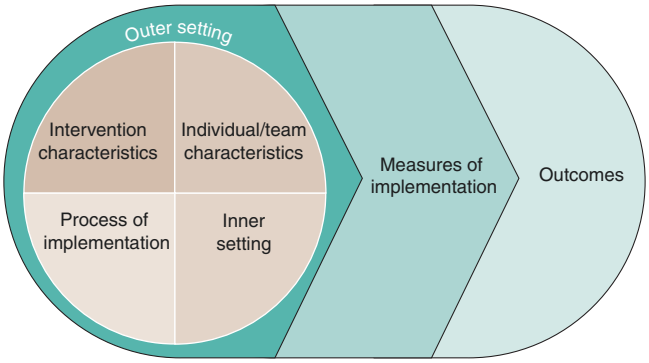

Fig. 39.4 Consolidated Framework for Implementation Research (CFIR). (Figure modified from Rojas Smith et al. [27])

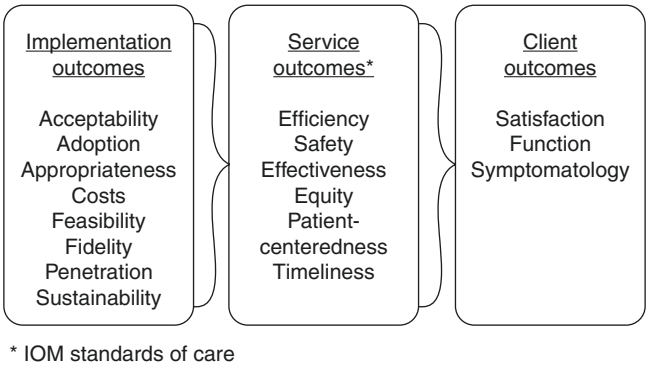

Fig. 39.5 Implementation, service, and client outcomes. (Reprinted with permission from Proctor et al. [29])

for Implementation Research or CFIR [26]. The basic structure of CFIR, shown in Fig. 39.4, defines five factors or domains that affect the quality of implementation [27, 28]. They are (1) outer setting, or the environment within which the implementation takes place (e.g., hospital or national policies or variations across surgical disciplines that may influence what is or is not possible to implement); (2) inner setting, or the characteristics of the organization such as the appetite for innovation or the organizational culture (e.g., rigid hierarchical organizations may not provide individuals the freedom to innovate); (3) intervention characteristics (e.g., the processes designed may be too complex or burdensome to implement even if they are supported by patients); (4) individual characteristics (e.g., the staff may not be motivated to implement the intervention or may lack general or intervention-specific capability); and (5) the implementation process (e.g., the communications about implementation may be disorganized, or there may be no systematic implementation plan).

Frameworks such as CFIR can be invaluable in elevating and analyzing the factors that affect the uptake, implementation success, and sustainability of an ERAS system in a particular department or hospital. It is important to recognize that the factors illustrated in Fig. 39.4 likely vary from site to site and from surgical specialty to surgical specialty. The CFIR provides a framework with measurement tools and instruments for a varied set of constructs in each domain. Using these instruments to identify the local barriers to implementation can help systems identify the key constraints that must be addressed to enhance the likelihood of successful implementation.

How do we measure the success of implementation? Implementation research defines a set of constructs called "implementation outcomes" that are separate and distinct from health outcomes. Figure 39.5 illustrates these outcomes [29]. As the figure suggests, implementation outcomes act as mediators or moderators to health or patient outcomes. Some desirable patient outcomes related to an effective ERAS program may be patient satisfaction, post-surgical complications, early discharge, or reduced patient readmissions [30]. As described previously, these outcomes depend both on the surgical process itself but even more so on a myriad of systems factors. Implementation outcomes provide a systematic approach for determining the variables that need to be considered and monitored in advance of the implementation and in a particular organizational context. For example, in a health system in which there is a rigid hierarchical organizational structure, ERAS—which requires trust, honest feedback and planning, teamwork, and communication—may not be acceptable to the surgical staff. In health-care systems where a single surgeon may circulate across multiple facilities, ERAS may not be feasible.

We suggest that studies measuring implementation outcomes and using frameworks such as CFIR to understand the factors that affect the successful implementation of ERAS will go a long way towards a deeper and more nuanced understanding of how to best engage clinicians in meaningful dialogue around change. These studies will build the knowledge of the targeted and generic service interventions that are the optimal precursors for successful ERAS implementation and sustained patient outcomes [31].

Adaptations and Improvement: The Model for Improvement and Implementation

Implementation outcomes and patient determinants are context-specific, and while studies measuring outcomes and CFIR constructs may enhance the body of knowledge about factors that need to be taken into account to implement ERAS successfully, the solutions to address these factors necessarily need to be local [32]. Interventions need to be adapted to address and overcome local barriers related to leadership, need for provider autonomy, variable trust levels, and other organizational contexts [33]. The process of adaptation does not happen magically; it requires the systematic and disciplined testing of a sequence of explicit adaptations

to arrive at a version of the intervention that makes sense to the local clinicians, is not thretening and is feasible and flexible [34]. Adaptations can be made in both the clinical and the implementation aspects of the intervention, but local leaders need to keep in mind the inherent tension between the fidelity to the clinical intervention itself (i.e., making sure the key mechanisms through which the intervention works are not modified) and, the need for local fit to clinicians' workflow. This ground up apporach will support local championship and engagement.

For a multicomponent intervention such as ERAS, clinical leaders should carefully consider each component of the ERAS protocol. They need to determine its adaptability, and what elements need to be adapted and customized, based on previous local knowledge in this specific commuinty about desired implementation steps to engage clinicians, and be open about how best to acknowledge and address the potential barriers. Some ERAS components such as the use of antibiotic prophylactics or avoidance of premedication prior to surgery may be considered core and not adaptable, but other components such as early mobilization and early oral nutrition post-surgery can and should be tailored to local and cultural and reimbursement practices. For example, the menus for postoperative oral nutrition could be designed to match the ethnic and cultural preferences of the patients. This approach helps to attenuate barriers to practice changes [35].

Adaptations for successful implementation can be guided by the Model for Improvement and Implementation (MFII), shown in Fig. 39.6 [36]. The left side of the figure is the well-known MFI and is used to guide the quality of improvement initiatives. This part of the model helps to determine which adaptations need to be made to the clinical intervention itself. By asking what changes need to be made to the intervention to improve the fit to the local context and department/hospital culture, the implementers can develop a site-specific version of ERAS that remains true to its core elements but is locally acceptable and feasible. But even an adapted intervention may not be successfully implemented if the organization is not ready or if staff members do not trust each other and are not motivated to change their workflow. The right side of the figure asks questions related to implementation barriers and seeks to develop and customize implementation strategies (e.g., leadership engagement, staff training and communications, team-building exercises, etc.) to address these barriers [35].

The Plan-Do-Study-Act (PDSA) cycle, which guides the iterative tests of change, binds these components together [37]. We suggest that clinical systems intending to imple-

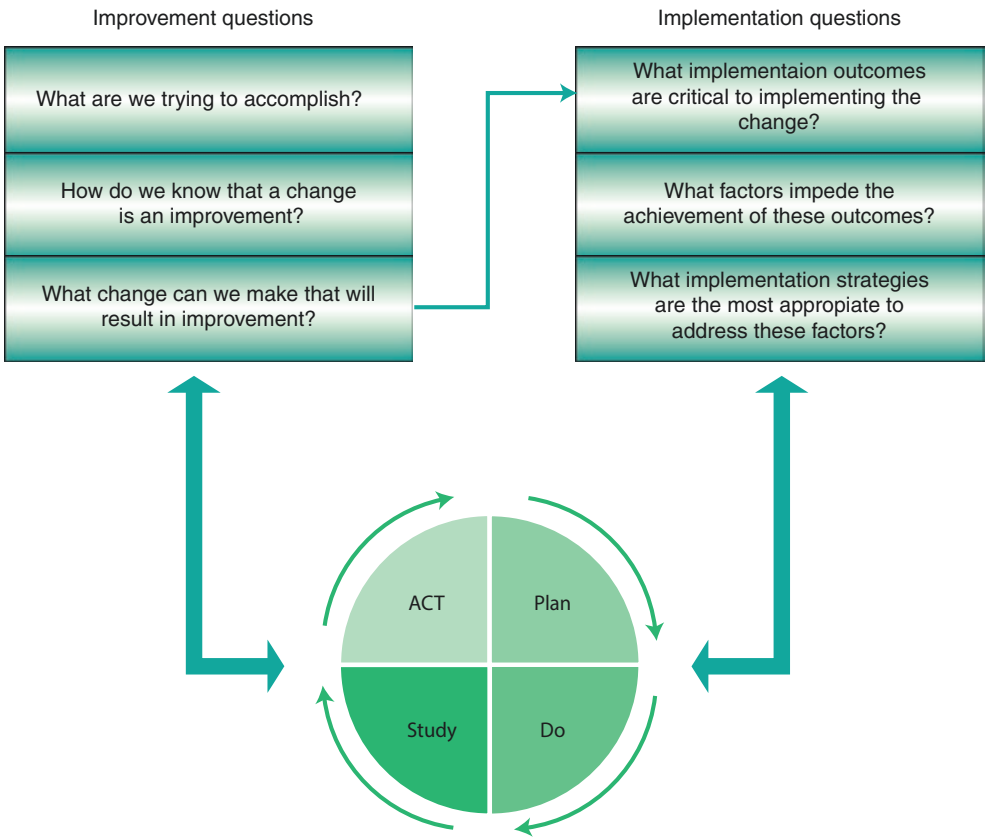

Fig. 39.6 Model for Improvement and Implementation (MFII). (Modified from Hirschorn and Ramaswamy [36])

ment ERAS use iterative PDSA cycles to adapt their intervention over time and allow for adequate time to refine the local iterative change model. We then encourage these health systems to use implementation methods to identify the implementation barriers and use the PDSA cycles to develop and test implementation strategies to address these barriers. Clearly, as Fig. 39.6 suggests, these are not independent activities.

Implementation challenges may require additional adaptations to the ERAS interventions, and these adaptations may result in the need for new implementation approaches. Figure 39.7 illustrates that an effective innovation (such as ERAS) is only one aspect of achieving successful and safe patient outcomes [38]. Effective evaluation of ERAS implementation and other components such a supportive hospital policies, patient centeredness, dedication to teamwork, focus on learning, etc. are all needed [15]. The MFII provides a structure to experiment and learn about how to strengthen all aspects of an ERAS system. Eight well-known quality tools are available to help organizations better understand and improve their ERAS processes [39, 40]. These tools include:

- Checklists
- Cause-and-effect diagrams
- Process flowcharts
- Pareto charts
- Scatter diagrams
- Probability plots
- Histograms
- Control charts

These tools help to visualize the system of care by mapping out the service lines at various levels of detail, helping to collect data to hone in on performance gaps, reviewing temporal and nontemporal performance patterns in the data that might cause deviation from consistent performance, quering as to what are the root causes for these deviations, and initiating PDSA cycles to address them. Training on these tools should be required for all members of the ERAS team before attempting to implement ERAS [41].

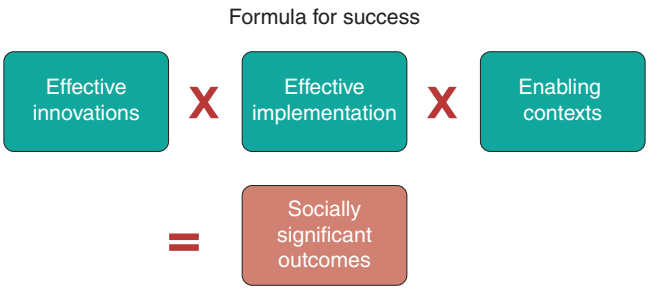

Fig. 39.7 Formula for successful implementation and update of clinical interventions [38]

Continuous Learning from Evaluation

It should be clear by now that successful implementation of an ERAS program requires not just the clinical studies to show that the intervention works in controlled study settings but also must be supported by a continuous organizational learning platform to understand how and what actually works in practice [42]. Evaluation methods for assessing the effectiveness of ERAS therefore need to determine not only whether patient outcomes have been achieved but also under what mechanism(s) they were achieved, for whom, and in what context. This requires the creation of an internal learning system that can document the results of the PDSA cycles described earlier, harvest learning, and share it with leaders in other facilities and systems so that knowledge about implementation becomes as pervasive as the knowledge about the intervention itself [16].

Learning is the acquired, relatively permanent or persistent change of behavior or behavior potential resulting from instruction, training, and practice (intentional learning) or experience (incidental learning). In 1984, Kolb described an experiential learning model, which argued that learning occurs through a cycle of reflective observations of concrete individual or team experiences in order to gain an understanding of what can be learned from each specific experience. This adaptive learning approach supports new ideas, which are applied to future experiences, renewing the cycle and supporting the professional joy and practice of the clinicians [43].

Figure 39.8 shows how a learning evaluation approach could work [44]. Each department or health system implementing ERAS uses the MFII to conduct PDSA cycles to create locally viable programs. The results of the PDSAs are discussed openly and regularly within each organizational microsystem in learning meetings, such as morbidity and mortality and staff meetings, and further adaptations and improvements are made, resulting in the next cycles of testing. At the same time, learning is shared across departments and hospitals in the system to build a robust system-wide knowledge base. This is hard, takes time to build trust and a requisite willingness to honestly evaluate each team and the entire microsytems' effectiveness, and does not happen automatically [45]. Infrastructure for common data collection, mechanisms for feedback and data sharing, and a joint and regularly articulated commitment to learning are all critical prerequisites for successful learning evaluation [46].

We suggest that the conduct of coordinated studies on ERAS programs that build on Peter Senge, Edwards Deming, and Don Berwick's work can drive clinical and continuous practice improvement, for example, by incorporating registries and/or pre-specifying quasi-experimental designs and creating conditions that support incremental learning across clinical microsystems using learning loops [47–49]. We propose that the aggregation of iterative learning loops within and across the various ERAS elements guided by national

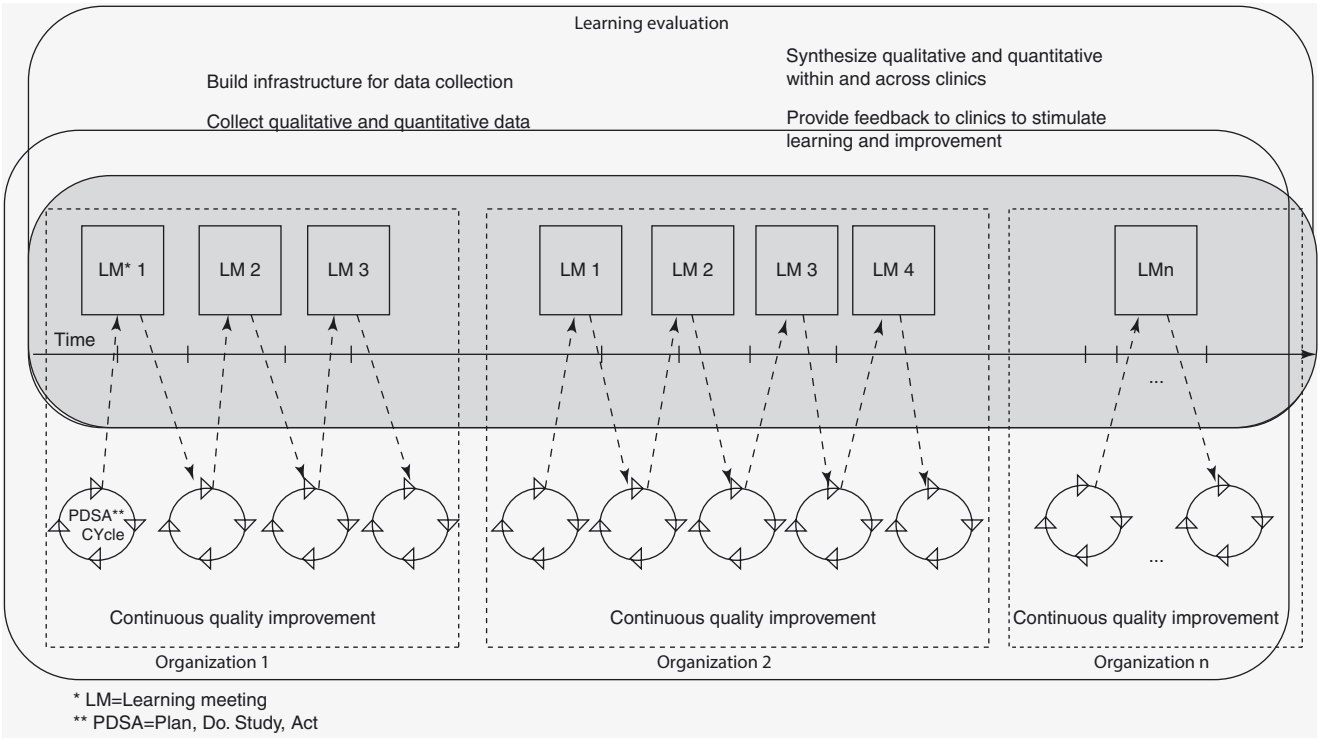

Fig. 39.8 A systems learning evaluation approach. (Reprinted with permission from Balasubramanian et al. [44])

and the international ERAS Societies can provide the conditions to rapidly accumulate knowledge, thus allowing the field to incorporate new understandings into new and improved structures and processes of care, consistent with the practices of double- loop learning [50].

Implementing ERAS: Some Foundational Considerations for Scale-Up and Sustainability

We have emphasized the need for ERAS implementation to be a system-wide approach, extending beyond the relatively narrow purview of the surgery itself and encompassing activities that affect the entire system up and downstream within which patient care is provided. For this to occur, and for the methods and tools of the design-focused implementation framework to be used effectively, some foundational elements of the system must be explicitly in place and be strengthened. We describe these principles now.

Principle 1: Building Trust for Organizational Resilience

The foundation of any successful cross-disciplinary collaboration is the building of a culture of trust. Trust must be based on more than merely being employees of the same organization because much of the state-of-the-science ERAS care requires groups of clinicians to work in teams, and patients must trust the overall team as well as its individual members [51]. Cultivating the trust of providers and patients in the teams delivering care would be simpler if those teams were well established, but many teams do not function well. The authors are aware from their experience how at times specialties regard each other in a negative manner, gaming of data, lying to each other and at times involving attending physicians who comment to residents that physicians in another specialty or based in the community were not "real doctors" [52].

Trust building is a slow, staged process and highly dependent on people's willingness to adapt a new professional intervention (sense-making) [53, 54], report honestly about their performance without fear (psychological safety) [55], accept input that may be critical of their work, and give their time in the pursuit of collective goals [56]. Frankel et al. [45] propose trust-ing building measures including:

1. Recognize that physician-physician relationships are consequential; they should be given the same level of attention and intention as patient-physician and interprofessional relationships.
2. Value differences in perspective; harness them as a resource. Disrespectful behavior in or around ERAS meetings that inhibits the participation of others, or the refusal to engage with others, eliminates the possibility of creating local adaption of ERAS protocols through dialogue, truth telling, and ultimately harming everyone, especially patients.

3. Notice the quality of the surgical team relationships when embarking on an ERAS program; be accountable and hold others accountable for creating patterns of respect, honoring profesional dissension and collaboration.

Physicians, like other people, can so focus on the technical aspects of their work that at times they do not notice the relational aspects. Confidence building requires years of collaborative effort. With increasing interpersonal familiarity comes interprofessional understanding and ultimately strong levels of commitment and engagement. Recent work in Alberta, Canada, suggests that thoughtful application of the Theoretical Domains Framework (TDF) through building trust, changing surgical care, and application of the Quality Enhancement Research Initiative (QUERI) to support system-wide implementation of an ERAS program for patients undergoing colorectal surgery has allowed successful implementation across multiple sites [31, 57].

Principle 2: Design Multi-stakeholder Collaboration and Authentic Learning Partnerships

The clinical microsystem provides a conceptual and practical performance and measurement framework for thinking about the organization and delivery integration of an ERAS program. Formed around a common patient service line or clinical need, and often embedded within larger organizations, a clinical microsystem is a small, inter-reliant group of people working together regularly to care for specific patient groups [10]. A clinical microsystem is characterized by a common aim, shared work processes, and a shared information environment. Optimally functioning ERAS clinical microsystems deliver the best quality healthcare services by deeply engaging all team members (both clinical and administrative) so they understand each process and outcome failures and near-misses and to also understand that what is most important to the people who make up the ERAS microsystem is key to continuous improvement [58]. The main driver and facilitator of learning within this environment are its uncompromising internal climate of learning, radical transparency and a culture of improvement. Awareness of the presence and support of the microsystem by its members, and support for its activity by the organization's leaders within which it is embedded, is therefore essential for the optimal functioning of the ERAS microsystem. Recent work shows that by building trust and local clinician engagement, ERAS colorectal guideline implementation can succeed across a health-care system resulting in patient outcome improvements, similar to those obtained in smaller stand-alone implementations [57]. The compliance in following the ERAS protocol in the study was 60%, with lower compliance in adopting postoperative care elements, thereby illustrating the greatest opportunity for practice changes across the health-care team.

Principle 3: Select and Train the ERAS Team

Effective ERAS implementation depends on the willingness of front line clinicians from diverse backgrounds to cooperate in varied clinical settings (i.e., clinic, operating theater, intensive care unit, surgical wards) toward a shared goal, communicate and work together effectively, and improve [59]. To achieve high reliability and consistent performance, each team member must be able to (1) anticipate the needs of the others [60]; (2) adjust to each other's actions and to the changing environment; (3) monitor each other's activities and distribute workload dynamically; and (4) have a shared understanding of accepted processes and how events and actions should proceed.

Effective ERAS implementation requires an understanding of how individuals and crews behave during ordinary and crisis situations. Implementers must discuss in a deliberate and entrusting manner how best to optimize patient flow, communicate, and negotiate available resources and develop skills in dynamic decision-making, interpersonal behavior, and teamwork that lead to safe outcomes [61].

The Team Strategies and Tools to Enhance Performance and Patient Safety (TeamSTEPPS) training program provides a standardized, evidence-based curriculum for ERAS team training [62]. TeamSTEPPS aims to teach four fundamental competencies that constitute teamwork (leadership, situation monitoring, mutual support, and communication) with the aid of patient scenarios, case studies, multimedia, and simulation [63, 64]. The TeamSTEPPS program applied to a variety of surgical settings has been shown to enhance teamwork within the operating room, improve operating room efficiency and reduce patient safety concerns in the process [65, 66]. Table 39.1 lists questions to consider when evaluating the performance of or ERAS teams.

Table 39.1 Questions to consider when evaluating the performance of an ERAS team

1. Is the team the right size and composition?
2. Are there adequate levels of complementary skills?
3. Is there a shared goal for the team?
4. Does everyone understand the team goals?
5. Has a set of ERAS spefic performance goals been agreed on?
6. Do the team members hold one another accountable for the group's actions and results?
7. Are there shared protocols and performance ground rules?
8. Is there mutual respect and trust between team members?
9. Do team members communicate effectively and regularily meet to review and debrief team perfomrance?
10. Do team members know and appreciate each other's roles and responsibilities?
11. When one team member is absent or not able to perform the assigned tasks, are other team members able to pitch in or help appropriately?

Principle 4: Establish Learning Collaboratives

Horizontal learning through a learning collaborative can be powerful took to improve ERAS learning, is an innovative and comprehensive approach to multidisciplinary "action research" that brings researchers, clinicians, and policy makers together to create a "community of practice" [67]. Evidence has shown that this "community of practice" builds trust, shares knowledge, and generates empirical evidence for use and spread of innovation of quality improvement initiatives. The approach represents a fundamental paradigm shift in that it actively seeks to bridge disciplinary silos and address knowledge gaps within and across the ERAS care delivery system. It can support the creation of an integrated research and implementation continuum stretching from the prehospital care phase to long-term wellness that can transform the care delivery services and spread innovation and uptake [68].

Principle 5: Integrate Practices from Human Factors Engineering into ERAS Microsystem Functioning

Design the physical environments for ERAS success that are based on sound human factors principles and constraints. Design for human cognitive failings and the impact of performance-shaping factors—fatigue, poor lighting, noisy settings, and so forth. Human factors usability evaluations and interventions should take place early in the design and system development processes. They should include tools such as work domain analysis, function allocation, probabilistic risk assessment, and usability testing, among others [69, 70].

Conclusions and Research Recommendations

The ERAS® Society has helped to show that enhanced recovery after surgery programs represents a paradigm shift in how surgical care is delivered and how changes in practice can be disseminated and implemented. These results rely on a new approach to meaninful teamwork, continuous audit, and support of data-driven change and improvement [19].

The real challenge remains how to translate these findings into new settings. Introducing and implementing ERAS practice is a complex challenge requiring what Deming calls the "profound knowledge" of improvement [71]. This involves four key components: (1) a deep knowledge of the system through which ERAS is delivered; (2) understanding system variation and the aspects of variation that can be tolerated or even required (as in adaptations) and those that need to be eliminated; (3) willingness to experiment to continually improve and be bold in advancing testable theories of improvement; and (4) engaging front line staff in the improvement process with transparency, truth telling, and trust building.

While emerging data is showing that thoughtful implementation of ERAS improves the opportunity for rapid, uncomplicated recovery after surgery with both short- and long-term benefits for patients, decreases patient readmission rates, and leads to significant cost savings, the benefits can never be realized at scale without a rapid diffusion of ERAS into mainstream using timely and robust methods for systems improvement and clinician engagement.

The nature of introducing complex systems such as ERAS is that small changes to inputs may produce large changes in results across the system. Therefore thoughtful implementation with an eye on key system leverage points reinforced by engaged learning communities may result in rapid acceleration of ERAS uptake once a "tipping point" is reached. By the same token, negative feedback loops may result in rapid deterioration of uptake from which systems may find it difficult to recover. The ERAS implementation tools require thoughtful application: They are not a hammer that can be universally employed in all circumstances. They are not an end in themselves. Instead they provide a starting place for systematic reflection, staff engagement, deepening trust and staff support, and enabling a deep and meaningful culture of continuous improvement. The process of implementing ERAS is iterative and cyclical. It should promote engagement among clinicians, staff, administration, and patients. It is systematic and based upon measurement and consultation with all stakeholders involved in the process.

Even if initial outcomes are achieved, the practice could determine how to produce an even better outcome or achieve it more efficiently and with less cost. Continuous quality improvement (CQI) is necessary and requires significant change in how surgical care is delivered. It explicitly seeks to be not only better but the best that a team can deliver under these circumstances. The staff ownership of the ERAS improvement process and adaptability of the intervention to address future quality outcomes are considered key strengths.

Research ERAS Road Map

This chapter has demonstrated that the tools and frameworks of ERAS design, implementation and improvement for implementing complex interventions in complex settings, as well as trust, truth telling among colleagues, and collaboration within the team are essential in developing sustainable and effective ERAS programs that not only affect patient outcomes but can also result in a transformed way of doing work. However, as mentioned previously, these tools do not offer a prefabricated solution to replicate innovative practices in complex settings. They can't be magically applied to ERAS without additional research to determine how they

need to be adapted to the particular contexts of different settings and surgical procedures [72].

We highlight below a number of unresolved research questions that need to be addressed about optimal ERAS uptake, scale, sustainability, and effectiveness. We organize these research questions into those that should be addressed in nearer term research and those that can be considered after the initial research phase is well under way.

Nearer-Term Research Questions

1. What does a generic ERAS process look like, and what are its variations? Based on the key principles of ERAS, can we develop a process and service map that can serve as a guideline for local implementation?
2. What are the critical moments of contact with patients in the ERAS process ("moments of truth")? What are the patient expectations at each of these moments, and what should be the measurable quality requirements (e.g., timeliness, consistency, compassion, etc.) that indicate that these expectations are being met?
3. What are the key barriers and organizational challenges for implementation of ERAS? How do we develop standard instruments that can easily applied to measure these barriers across surgery types and settings?
4. What kinds of implementation strategies are most effective? How do they vary by different organizational, insurance coverage, and cultural differences in order to address these barriers? How do we test these implementation strategies rapidly without the need for complex, expensive, and time-consuming research designs?
5. What kinds of methods are most appropriate for determining what aspects of the ERAS process can be adapted? What aspects need to be delivered with fidelity and which can succeed with low fidelity?
6. What are the mechanisms for harvesting, documenting, and sharing best practices related to ERAS implementation that can enable rapid learning across large healthcaresystems and stakeholders?

Longer-Term Research Questions

1. Since ERAS is a complex intervention consisting of multiple components, how do we determine the relative contribution of each component in achieving ERAS outcomes? How do we understand the interactions between these components and their relative contributions?
2. What are the mechanisms by which the various components of the ERAS process (e.g., clinical processes, operational processes, relationships among team members) contribute to lasting patient outcomes? How can an understanding of these mechanisms lead to better design of future ERAS programs?
3. What generic service interventions (e.g., system-strengthening interventions such as leadership development, communication processes, transparency organizational dashboards, equitable decision-making, etc.) need to be in place for successful ERAS programs to take root and be owned by clinicians? What are the best methods for developing, incentivizing, and implementing these interventions within the context of ERAS?
4. To what extent can programs such as ERAS facilitate change in the organizational culture of surgery departments that can result in long-term transformation to the way effective surgical, anesthetic and nursing care is provided? What are the mechanisms by which this transformation can take place?
5. What are the key elements of ERAS that can be adapted for low resource countries settings? What can be done to rapidly accelerate this uptake, scale-up, and sustainability given wide differences in cultures and work-related values [73]?

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Part VIII

Specialty-Specific Enhanced Recovery Programs

ERAS in Colorectal Surgery

40

Ulf O. Gustafsson

Background

It is not a coincidence that the thoughts and theories about enhanced recovery first came into the field of colorectal surgery. The average age at diagnosis with colorectal cancer is generally high, and most of the patients are scheduled for major surgery with a high risk of complications. Although the outcome from surgery in the end of the 1990s and the beginning of the twenty-first century was improved due to better surgical technique and improved organizational structure, patients still suffered from slow recovery, high morbidity rates, and prolonged hospitalization up to mean 14 days [1–3].

One of the main problems was the absence of general guidelines for perioperative care. Traditional perioperative care was simply based on hands-on experience passed on between surgeons for generations. This not only resulted in different types of practice in various clinics but also limited the possibility of congruent audits of perioperative processes and outcomes between different surgical centers. Due to the lack of congruent outcome definitions, some studies reported only major complications, while others divided complications into local, general, and surgical. Different definitions for the same complication further hampered the interpretation of results after surgery. As a consequence, there was a vast diversity in the way postoperative complications were reported, and significant variations in complication rates in the surgical literature made interpretation and evaluation difficult. For example, morbidity after colorectal surgery was reported to be 10–20% [4] in some studies but 45–48% [5, 6] or even 8–75% [7] in others.

Due to the lack of congruence in perioperative care across sites, the unsatisfactory recovery rates, and diverse quality in terms of reporting outcomes, there was a need for new perioperative regimens, other than the currently practiced traditional perioperative care.

Implementation of ERAS Protocols

When the fast-track pioneer Henrik Kehlet and his group from Denmark first published data on enhanced recovery with patient discharge 48 hours after colonic surgery (rather than 7–14 days in traditional care) with an accelerated stay program [8], many colorectal surgeons were taken by surprise and even disbelief. Could this really be true? This group actually claimed improvement by reducing length of stay (LOS) to one-seventh of the then standard time. The results would however soon be repeated and confirmed by other colorectal groups in Europe and the USA.

Inspired by the work of Kehlet et al. and due to the lack of consistency in perioperative audit and large differences in rates of outcome after surgery in different surgical centers, the enhanced recovery after surgery (ERAS) study group collaboration was established in 2000. The group later developed the ERAS® Society in 2010 (see Chap. 65). The aim with the collaboration has been not only to develop, improve, and spread the ERAS protocol but also to implement the same perioperative regimen in all participating centers resulting in comparable outcomes. A central database [9] for prospective collection of perioperative data (today more than 300 different variables) was specifically designed to enable such comparisons. The application of strict criteria for collecting the different variables in the database enables congruently defined and more reliable audits of pre-, peri-, and postoperative outcomes. Since nonphysicians are shown to be better data collectors and not underreporting morbidity like many clinicians do [10, 11], trained nurses prospectively collect the data and register it in the database.

Ever since the start of the ERAS collaboration, more than a hundred colorectal centers throughout the world have been trained in ERAS implementation programs and register

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peroperative data in the international database. Today, the database has more than 70,000 registered patients.

The ERAS Protocol and Number of Interventional Items

Several studies have demonstrated that the ERAS programs compared with traditional perioperative care is associated with earlier recovery and discharge after colorectal resection. When comparing the ERAS protocols with traditional care in meta-analysis, there is a significant reduction in risk ratio (RR) for postoperative morbidity in patients undergoing colorectal surgery within an ERAS program of 48%; RR, 0.52 (0.38–0.71) [12]; and length of stay, −2.51 days (−3.54 to −1.47) [13].

However, current evidence in favor of the ERAS protocol applies for the whole protocol and not for every single item within it. Data on ERAS protocols have so far mostly been based on diverse programs with a variety of interventions depending on what the authors regard as standard of care or their choice of elements in their local protocol. In one systemic review [7], studies employing between 4 and 12 ERAS items were reported. Because of this variation, there has been an ongoing debate about the number of ERAS items that should be used in the ERAS protocol. In order to reach consensus on this matter, the ERAS® Society guidelines present recurrent updates that are based on all elements that have been shown to impact outcomes. The guidelines present not only the evidence of all such elements in the entire protocol but also evidence for each single item.

In the latest published guidelines (2018), the number of ERAS items is 25, each of them recommended according to either *strong recommendations* or *weak recommendations.* Recommendations are based on quality of evidence (*high*, *moderate*, *low*) but also on the balance between desirable and undesirable effects and on values and preferences of practitioners. Thus, strong recommendations may be reached from low-quality data and vice versa (Fig. 40.1).

Although the level of evidence differs between different ERAS items, the current opinion among ERAS collaborators is that they all should be used in order to truly follow the ERAS protocol. To better understand why all ERAS items may be important, a more detailed presentation of the content of the ERAS protocol is needed.

ERAS Items and Their Importance in Optimizing Perioperative Care in Colorectal Surgery

The different ERAS items or interventions are divided into four categories: preadmission, preoperative, intraoperative, and postoperative items (Figs. 40.1 and 40.2). This scheme helps to get a structured overview of the protocol. But above all the protocol overview is provided in order to compare, analyze, and understand outcome data from the surgery. For example, compliance to the protocol is mostly measured for scientific reasons and is analyzed with preadmission, preoperative, and intraoperative data, since postoperative data are in general under the control of the caregiver. Postoperative elements, on the other hand, can be considered in part as outcome measures and are usually hard to achieve unless there has been compliance with the previous elements. While the postoperative elements are important for clinical reasons, for scientific reasons they may introduce bias into the calculations.

Preadmission Items

The fact that patients should be well-informed before undergoing major surgery may sound obvious. But if *preadmission information*, education, and counseling are not conducted in a structured order, there is a high risk of insufficient patient awareness and engagement. Since patients fear the unknown, proper and complete information may reduce anesthesia- and surgery-related anxiety, and this may impact the subsequent sensation of pain [14]. Detailed, procedure-specific, and patient-centered information has shown to have a positive impact on length of stay and postoperative outcomes [15, 16]. Therefore, patients should receive dedicated preoperative counseling routinely. Although there is a strong belief that preoperative *medical optimization* is important for an optimal surgical outcome, the use of current preoperative risk assessment scores proposed in the literature is limited. There is simply not good enough evidence for any of the assessment tools for a recommendation. However, general preoperative optimization includes many different areas of possible improvement. For example, patients who smoke have an increased risk of intra- and postoperative complications [17], and although the optimal preoperative intervention, duration, and intensity are unknown, 4–8 weeks of abstinence appear necessary to reduce respiratory and wound-healing complications [17]. Alcohol abuse increases postoperative rates of infections, and therefore preoperative abstinence of 4 weeks is recommended [18].

Although, poor preoperative physical status has been shown to be a risk factor for serious postoperative complications and prolonged disability [19] and that *prehabilitation* (interventions that promote physical and psychological health to reduce the incidence and severity of postoperative impairments) show promising results in some studies [20], the current recommendation is still weak. This is, however, a growing research field with several ongoing studies (see Chap. 10).

Poor nutrition has for long been a neglected problem in colorectal surgery. The risk of complications is increased in patients with unintentional weight loss of 5–10% or more,

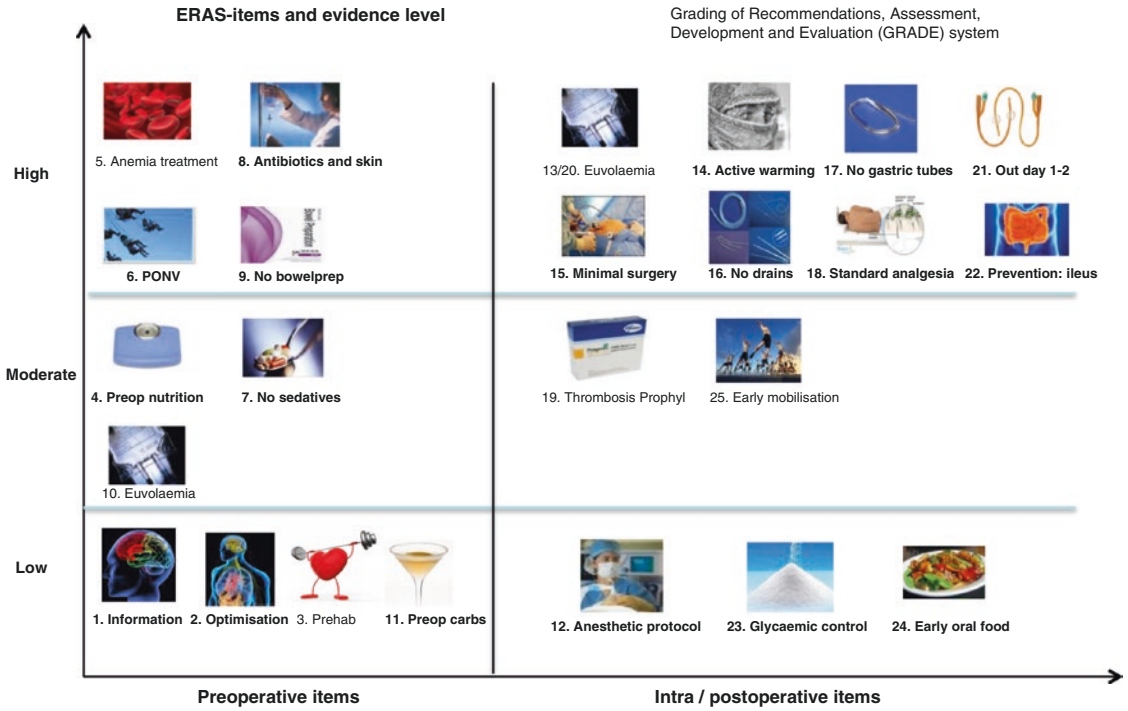

Fig. 40.1 ERAS items

Preadmission Items:

1. Preadmission information and counseling
   Quality of evidence: Moderate
   Recommendation grade: Strong
2. Preoperative optimization
   Quality of evidence: Low
   Recommendation grade: Strong
3. Prehabilitation
   Quality of evidence: Low
   Recommendation grade: Weak
4. Preoperative nutritional care
   Quality of evidence: Moderate
   Recommendation grade: Strong
5. Treatment of anemia
   Quality of evidence: High
   Recommendation grade: Strong

Preoperative Items:

6. Prevention of nausea and vomiting (PONV)
   Quality of evidence: High
   Recommendation grade: Strong
7. Pre-anesthetic nonsedative medication
   Quality of evidence: Moderate
   Recommendation grade: Strong
8. Antimicrobial intravenous (IV) prophylaxis and skin preparation
   Quality of evidence: High
   Recommendation grade: Strong
9. Avoiding bowel prep in colonic surgery
   Quality of evidence: High
   Recommendation grade: Strong

10. Preoperative euvolemia in fluid and electrolyte therapy
Quality of evidence: Moderate
Recommendation grade: Strong

11. Preoperative carbohydrate loading
Quality of evidence: Low
Recommendation grade: Strong

Intraoperative Items:

12. Standard anesthetic protocol
Quality of evidence: Low
Recommendation grade: Strong

13. Balanced fluid and electrolyte therapy
Quality of evidence: High
Recommendation grade: Strong

14. Preventing intraoperative hypothermia
Quality of evidence: High
Recommendation grade: Strong

15. Minimally invasive surgery
Quality of evidence: High
Recommendation grade: Strong

16. No drainage of the peritoneal cavity and pelvis
Quality of evidence: High
Recommendation grade: Strong

Postoperative Items

17. Avoiding nasogastric intubation
Quality of evidence: High
Recommendation grade: Strong

18. Standardization of postoperative analgesia
Quality of evidence: High
Recommendation grade: Strong

19. Thromboprophylaxis
Quality of evidence: Low/High
Recommendation grade: Strong

20. Neutral balanced fluid and electrolyte therapy
Quality of evidence: High
Recommendation grade: Strong

21. Limited time of urinary drainage
Quality of evidence: High
Recommendation grade: Strong

22. Prevention of postoperative ileus
Quality of evidence: High
Recommendation grade: Strong

23. Postoperative glycemic control
Quality of evidence: Low
Recommendation grade: Strong

24. Postoperative nutritional care
Quality of evidence: Low
Recommendation grade: Strong

25. Early mobilization
Quality of evidence: Moderate
Recommendation grade: Strong

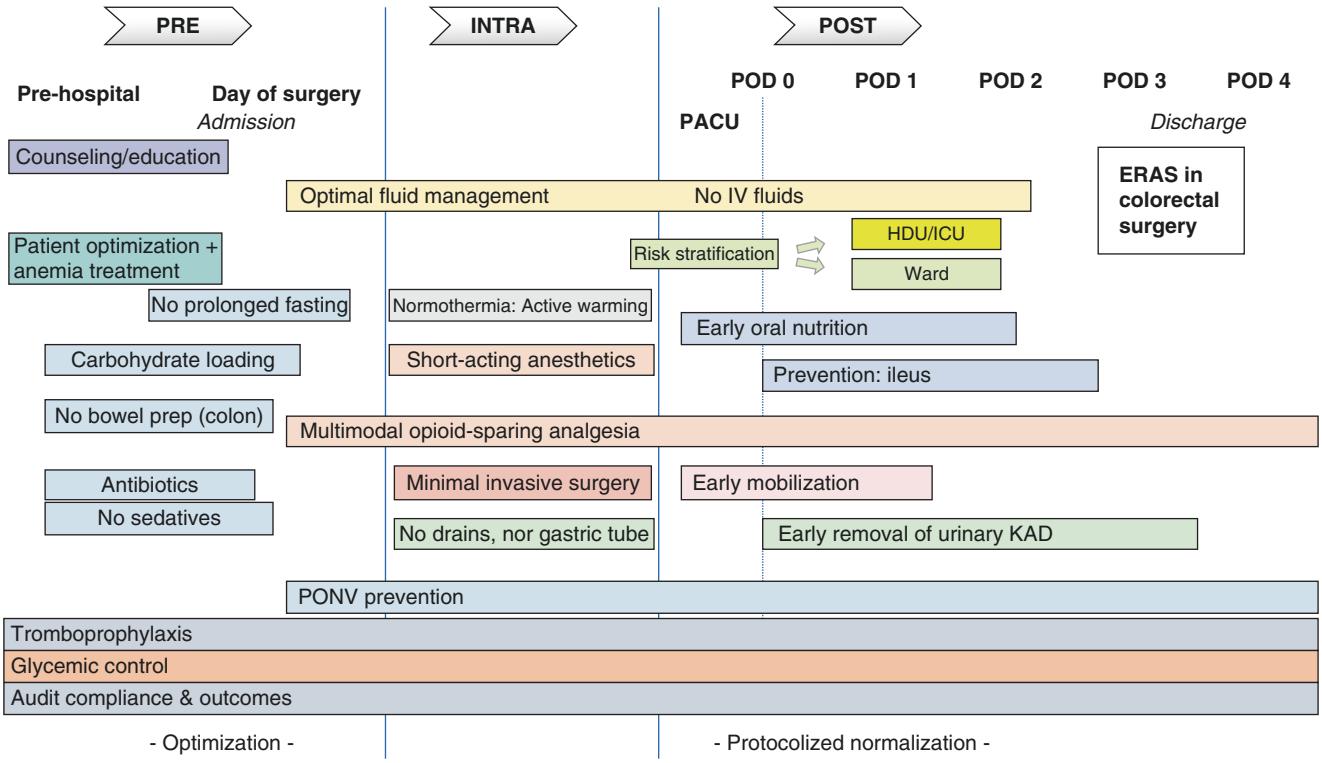

Fig. 40.2 General ERAS principles for colorectal surgery. PACU postanesthesia care unit, IV intravenous, HDU high-dependency unit, ICU intensive care unit, KAD indwelling urinary catheter, PONV postoperative nausea and vomiting

and these patients benefit from preoperative nutritional treatment [21]. Preoperative routine nutritional assessment offers the opportunity to correct malnutrition and should be offered. Patients at risk of malnutrition should receive nutritional treatment, preferably using the oral route for a period of at least 7–10 days.

Most of the patients scheduled for colorectal surgery suffer from iron deficiency because of blood loss or chronic inflammation; many of them show *anemia,* which may be a risk factor for all kinds of complications and mortality [22]. The most common traditional treatment for perioperative anemia has been blood transfusions. Recently, however, transfusions have been questioned because of increased risk of surgical site infection, septic shock, and possibly also decreased 5-year survival [23]. It is therefore essential to optimize the patient's Hb concentration preoperatively. Since many colorectal surgical patients will either not respond to oral iron due to chronic illness or severe loss of appetite, intravenous (IV) iron infusion should be given to these patients.

Preoperative Items

Postoperative nausea and vomiting (PONV) affects up to 50% of all surgical patients and up to 80% of patients who are at high risk for developing these complications (female gender, those with a past history of PONV or motion sickness, and non-smokers) [24]. A multimodal approach to PONV prophylaxis should be used in all patients scheduled for colorectal surgery. A 2-drug combination prophylaxis using first-line antiemetics is recommended for patients with 1–2 risk factors, and if there are ≥2 risk factors, 2–3 antiemetics are recommended. Overall, postoperative analgesia by opioid-sparing multimodal techniques significantly reduces the risk of postoperative PONV.

Traditionally, preoperative patient anxiety has been treated with *long- or short-acting sedative medication.* However, anxiolytics such as benzodiazepines may increase the risk for impaired postoperative motor function with a negative impact on mobilization. Although preoperative education can reduce patient anxiety to an acceptable level without the need for anxiolytic medication in most cases, some patients may need multimodal medication such as acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and gabapentinoids to decreased postoperative pain and opioid consumption.

There is a broad body of evidence and consensus that *antibiotic prophylaxis* reduces postoperative surgical site infections (SSI) [25]. A remaining question is if IV or oral, or both, should be given as prophylaxis. The question is further complicated by the controversy about the role of oral bowel

preparation and the combination of antibiotics for the development of surgical infections. Most of the information about the use of oral antibiotics is from studies where patients are treated with bowel preparation, and there is currently not enough evidence to support oral antibiotic decontamination alone in patients undergoing surgery without prior bowel preparation. In patients given bowel preparation, however, additional benefits of administering oral to IV antibiotics have been reported. This treatment is usually given 18–24 hours before surgery, and its effect is attributed to inhibiting opportunistic pathogens inside the colonic lumen before opening the colon. Today, most centers worldwide use IV antibiotics only, given within 60 minutes before incision as a single-dose administration to all patients undergoing colorectal surgery. No benefit has been shown for repeated administration.

Chlorhexidine-alcohol-based preparations should be used for *skin disinfection*. Evidence is insufficient to support advanced measures such as antiseptic showering, routine shaving, and adhesive incise sheets.

Avoidance of *mechanical bowel preparation* (MBP) has been one of the cornerstones in ERAS protocols from the start. The reason for this is that bowel preparation causes dehydration and discomfort and thereby counteracts enhanced recovery. The use of MBP makes patients lose up to 2 L of total body water as a consequence, which is important since patients should reach the anesthetic room in as close a state to *euvolemia* as possible, and any preoperative fluid and electrolyte excesses or deficits should be corrected.

Although it is part of ERAS recommendations, avoiding mechanical bowel preparation for coloinic resections has repeatedly been questioned, especially in the USA where avoiding MBP was never fully accepted. However, in the most recent and largest meta-analysis [26] of 36 studies (21,568 patients) comparing adult patients receiving MBP versus with those receiving no MBP, MBP was not associated with any significant difference in any of the major important outcomes. There was no difference in anastomotic leak rates (OR 0.90, 95% CI 0.74 to 1.10), surgical site infection (OR 0.99, 95% CI 0.80 to 1.24), mortality (OR 0.85, 95% CI 0.57 to 1.27), or hospital length of stay (overall mean difference 0.11 days, 95% CI -0.51 to 0.73), when compared with no MBP. This was also true when only evidence from randomized controlled trials (RCTs) was analyzed. Thus, avoiding MBP in colonic surgery is still advocated.

The situation is different in rectal surgery. In these operations, MBP may be used since the effect of remaining stools in a diverted colon is uncertain.

Overnight fasting is obsolete, and patients should be recommended to drink clear fluids until 2 hours before anesthesia and surgery. Solids should be withheld for 6 hours. The idea to offer patients *oral carbohydrates* (complex CHO-maltodextrin, 12.5%, 285 mOsm/kg, 400 ml 2–3 hours before induction of anesthesia) is based on evidence of improved preoperative well-being, reduced postoperative insulin resistance, decreased protein breakdown, and better maintenance of lean body mass and muscle strength, as well as beneficial cardiac effects. In patients with diabetes, there is still uncertainty if oral carbohydrates can be recommended or not.

Intraoperative Items

For many years, the lack of a *standardized anesthetic protocol* where each anesthesiologist treated patients according to their own preferences resulted in a heterogeneous recovery outcome. Within the ERAS protocol, the use of short-acting anesthetics such as propofol for induction of anesthesia, combined with short-acting opioids such as fentanyl, alfentanil, and sufentanil, minimizes residual anesthetic effects at the end of anesthesia. This regimen together with intraoperative cerebral monitoring to improve recovery and reduce the risk for postoperative delirium and monitoring of the level and complete reversal of neuromuscular block is mandatory in ERAS anesthetics.

Since the start of the ERAS collaboration, *avoiding excess intraoperative fluids* has been a cornerstone in perioperative care. In most of the published works from ERAS cohorts so far, excess of intra- and postoperative fluids has been shown to be a determinant for poor outcome. On the other hand, data from these studies derives from a time when it was not uncommon that patients were treated with 6–7 L of fluids on the day of surgery in traditional care.

Today, awareness of the importance of intraoperative fluid restriction is widespread, also outside the ERAS protocol. Currently, the focus in fluid therapy should be to maintain fluid homeostasis, avoiding both fluid excess and organ hypoperfusion, where fluid excess leading to perioperative weight gain more than 2.5 kg should be avoided. Goal-directed fluid therapy is recommended in high-risk patients, but for most patients a perioperative near-zero fluid balance approach is enough for adequate intraoperative treatment.

Even a mild *intraoperative hypothermia* (<36 °C) in patients has been associated with adverse effects such as vasoconstriction, increased afterload, myocardial ischemia and cardiac arrhythmias, reduction in splanchnic blood flow, and reduced drug biotransformation [27]. Therefore, reliable temperature monitoring should be undertaken in all colorectal surgical patients, and methods to actively warm patients to avoid temperatures below 36 °C (IV and irrigation fluids and forced air warming blankets and devices) to avoid hypothermia should be employed.

Surgical Approach

Minimally invasive procedures have had a fundamental impact on colorectal surgery and in many ways have paved the way for many of the items in the ERAS protocol. Both the very early oral food and early postoperative mobilization were first shown to be possible in laparoscopic colorectal surgery in the end of the 1990s. Several studies [28–30] of laparoscopic versus open surgery for colorectal cancer favor laparoscopy for recovery, length of hospital stay, blood loss, and complications. There is no evidence of an oncological disadvantage—at least not in colonic surgery—whereas data from rectal cancer procedures still are uncertain. The impact of both the ERAS protocol and laparoscopic surgery on outcome was investigated in a multicenter RCT: the LAFA study [31], where regression analysis showed that laparoscopic surgery was the only predictive factor to reduce hospital stay and morbidity but also that the best outcomes with the least impact on the immune system were in the group receiving both minimally invasive surgery and enhanced recovery protocol.

Robotic surgery is a more recent form of minimally invasive surgery. So far, small cohort studies show promising results (fewer conversions, shorter length of stay) in rectal cancer surgery. However, a large randomized trial [32] showed no differences in any clinical outcomes compared to laparoscopic surgery, while robotic surgery was not as cost-effective.

The use of *drain* in the peritoneal or pelvic cavity is today mostly of historical interest since drains show no effect on clinical outcome and should not be used routinely.

Postoperative Items

The aim of using *nasogastric (NG) tubes* has been to reduce postoperative discomfort from gastric distension and vomiting. There is, however, solid data showing that NG tubes have no positive but instead a series of negative effects. Avoiding NG tubes decreases risk of pulmonary complications and delay of important nutrition in the postoperative period. Thus, nasogastric tubes should not be used routinely postoperatively. If inserted during surgery, they should be removed before reversal of anesthesia. However, care should be taken. In patients with postoperative paralytic ileus, decompression of the stomach may be important to reduce the risk of aspiration, and this still remains a valid indication for its use.

Within the ERAS protocol, a multimodal approach to postoperative pain management is advocated. There are several ways to achieve *postoperative analgesia.* They all strive to avoid opioids since opioid-sparing techniques are associated with early mobilization, fast return of bowel function, fewer complications, and a reduction in LOS.

In fact, using a multimodal approach with several analgesia techniques results in the best pain outcomes. Paracetamol and NSAIDs are two basic opioid-sparing components in multimodal analgesia. Addition of other drugs, such as lidocaine infusions, alpha-2 agonists such as dexmedetomidine, ketamine, magnesium sulfate, high-dose steroids, or gabapentinoids are frequently used. Medical treatment should be combined with epidural blockade, spinal anesthesia, lidocaine infusions, or abdominal blocks depending on patient status and which surgical approach—open or minimally invasive—has been used during the operation. Avoiding pain is one of the key factors to achieve patient satisfaction and shortening of hospital stay and should be taken seriously, even early in the postoperative period.

Ever since *thromboprophylaxis* was introduced in major surgery, the duration of the treatment has been a subject for discussion. Risk factors for thrombosis include ulcerative colitis, advanced malignancy (Stage III + IV), hypercoagulable state, steroid use, advanced age, and obesity. This implies that most patients undergoing colorectal surgery should be treated with low-molecular-weight heparin (LMWH) and compression stockings and/or intermittent pneumatic compression (ICP) during hospitalization. The level of evidence is low for the commonly used prolonged (28 days) treatment with LMWH. However, since thrombosis and especially its sequalae are serious complications, and there is a lack of data showing that there is no risk or benefit from shorter duration or no prophylaxis, the recommendation for prophylaxis with LMWH remains once daily for 28 days after surgery.

Postoperative fluid management follows the path of the intraoperative target for the treatment, namely, to keep the patients normovolemic. This almost always means that IV fluids should be discontinued postoperatively. Instead, patients should be encouraged to drink as soon as they are awake and free of nausea after the operation, and an oral diet can usually be started within 4 hours after surgery.

In colorectal surgery, *urinary drainage* has been standard postoperative treatment for prevention of urinary retention and monitoring of urine output. The risk of urinary retention after major surgery is reported to be between 10% and 20%, where male gender and postoperative epidural analgesia are important independent predictors of retention. In the perioperative setting, oliguria is traditionally defined as a urine output <0.5 ml/kg/h, and additional fluid is often administered to reach output above this target. There is, however, little evidence to support this regimen. Recent reports show that less than half of this urinary output is well tolerated among patients [33]. With the acceptance of permissive postoperative oliguria, the need for monitoring of urinary output is hardly necessary anymore. In addition, prolonged treatment with urinary catheters increases the risk of urinary

infections. Because of these insights, routine transurethral catheterization is recommended for shorter periods of time. Patients at low risk should have routine removal of catheters on the first day after surgery, while patients with moderate or high risk require catheterization for up to 3 days.

Postoperative ileus is one of the major obstacles for fast recovery and causes patients to suffer from severe discomfort and delayed discharge. Thus, *prevention of ileus* is a key objective of enhanced recovery protocols. Many of the items within the protocol support return of gut function and thereby indirectly counteract prolonged postoperative ileus, limiting opioid administration through application of multimodal analgesia techniques, eliminating routine nasogastric tube placement, use of minimally invasive surgery, and maintaining fluid balance including goal-directed fluid therapy. To more specifically target the problem of ileus, peripherally acting μ(mu)-opioid receptor (PAM-OR) antagonists such as alvimopan, methylnaltrexone, naloxone, and naloxegol have been shown to accelerate gastrointestinal recovery. Chewing gum has been used for many years, but recent studies show a lack of effect. On the other hand, bisacodyl, magnesium oxide, and coffee all have some positive effects counteracting established ileus.

So-called pseudodiabetes of injury or insulin resistance affects every patient going through major surgery and persists for several weeks. Hyperglycemia caused by perioperative insulin resistance is a risk factor for complications and should therefore best be avoided. Treatments such as preoperative carbohydrates, mid-thoracic epidural analgesia, and early feeding all help minimize insulin resistance. Although these interventions reduce insulin resistance and hyperglycemia, insulin should be used judiciously to maintain blood glucose as close to normal as feasible within the available resources.

Early oral diet has been shown to be safe 4 hours after colorectal surgery. Since spontaneous food intake rarely exceeds 1200–1500 kcal/day [34], additional oral nutritional supplements (ONS) should be offered. Recently several studies show improved outcome if malnourished patients are treated with so-called immunonutrition. These are ONS with the addition of combinations of L-arginine, L-glutamine, ω(omega)-3 fatty acids, and nucleotides. Even if the level of evidence in favor of immunonutrition is low, some centers now use this regimen in their daily practice.

To have the patient return to normality as soon as possible after the operation, enhanced recovery protocols support *early mobilization* after surgery. Although available studies on mobilization show conflicting results, it is a general belief that prolonged immobilization is associated with a variety of adverse effects—such as developing pulmonary complications, decreased skeletal muscle strength, thromboembolic complications, and insulin resistance—and patients should therefore be mobilized. Patients should be out of bed at least 2 hours the same day as the operation. Postoperative day one, the aim is to increase the time out of bed to 6 hours.

Audit and Compliance to the Protocol

For decades, major surgery has been performed without proper and reliable evaluation of the outcome. In the past, consensus about best perioperative care has been lacking, and the knowledge about how to improve results has been poor. In the last decades, however, strategies to improve this gap in knowledge have emerged. One such successful strategy has been to start to structure perioperative care and building platforms for audit, implementation, and further research. The ERAS Study Group and Society has led this development by constructing a common database for interactive audit: the ERAS® Interactive Audit System. The main purpose of a common database is not only to benchmark outcomes from surgery with other centers, it is also to receive continuous feedback in order to improve perioperative care and to implement changes and improvements in the local unit. The feedback informs the local team how well they are complying with the standardized perioperative protocol by entering consecutive patients in the registry. Audit and feedback has its best effects when done repeatedly (monthly), delivered by colleagues, and given both in writing and verbally, with specific targets for change and for multifaceted interventions.

Many units claim that they are using the ERAS protocol, but only a few can show documentation of the details needed to show it is actually being done. Thus, most of the early works within the enhanced recovery research field were published without measurements and calculations on compliance. Did the patients actually fulfill all the items that they were intended to? What was the outcome if they did not? This is crucial since it has been shown that there is more or less a dose-respondent relationship between compliance to the protocol and short-term outcome from colorectal surgery [35] (Fig. 40.3).

Furthermore, when reviewing data to analyze long-term survival, it was found that for patients with ≥70% compliance to ERAS items, 5-year colorectal cancer-specific death was lowered by 42%, HR 0.58 (0.39–0.88, cox regression) compared to all other patients (<70% adherence) [36].

Data on compliance to the protocol is essential in order to conduct research within the ERAS field, but it is also necessary when evaluating the perioperative work at the clinic. Most centers with an active ERAS environment can reach 70% compliance, which seems to be an important cutoff for improved outcome. With detailed information and feedback on compliance of each item, often a relatively small but correctly targeted effort is required to improve the ERAS compliance and outcomes in a given institution.

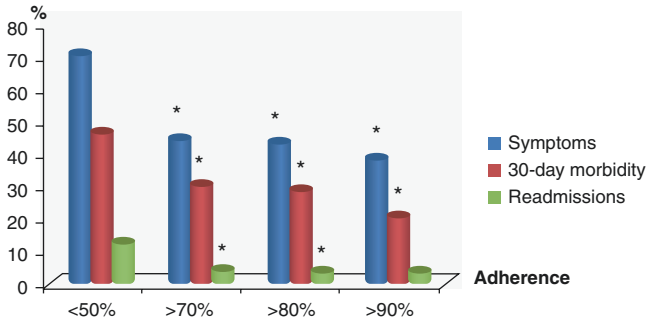

Fig. 40.3 Association between adherence to the ERAS protocol and postoperative outcomes. The proportion with adverse postoperative outcomes (symptoms delaying discharge, 30-day major and minor morbidity and readmissions) was reduced with increasing adherence to the ERAS protocol (>70%, >80%, >90%), compared to low ERAS adherence (<50%). Multiple logistic regression, adjusted for age, gender, ASA, body mass index (BMI), type of operation, and laparoscopic surgery. Symptoms: unspecified fever, pain, fatigue, constipation, dizziness, and diarrhea causing delay of discharge. Readmission: clinical status requiring in-hospital treatment. ∗Significant difference. (Adapted from Gustafsson et al. [35])

The ERAS Protocol in Colorectal Surgery, Future Perspectives

Within surgery, few subspecialties have evolved so much the last 10 years as colorectal surgery. The awareness of the benefits of colorectal cancer screening among the population is increasing, although in some countries that are running such programs, compliance to screening currently is only approximately 50%. New future techniques will allow for tumors to be detected in far more early stages, and as such they can then be removed with endoscopic methods. Techniques such as endoscopic submucosal dissection (ESD) can manage to resect increasingly more advanced tumors, and in some centers major resection surgery has decreased by 25%. In rectal cancer treatment, radiotherapy techniques are constantly improving. Up to 15% of patients who previously had both radiotherapy and major surgery now show complete response after radiation alone and may avoid surgery. The rate of such treatments will probably increase in the future.

In the field of inflammatory bowel disease (IBD) treatment, new drugs with immunological mechanism of action will probably further decrease the need for surgery. The research on colonic bacteria has completely exploded in recent years. New data on the bacterial genome using metagenomics and metabolomics will open the door for new screening tools and treatment methods in all colorectal diseases.

Even if the need for resection surgery will decrease in the future, there are still patients who will require major surgery. Also, for major operations there have been remarkable developments in recent years. Laparoscopic colorectal surgery is currently well implemented worldwide and shows equal or better short-term outcome compared to open surgery. If the development of laparoscopic surgery took some time to be fully accepted in the colorectal community, robotic surgery was approved in many centers much faster. Even if the current evidence in favor of robotic surgery is sparse, many believe that this technique will dominate in all surgical procedures in the future. Furthermore, intense research in the field of artificial intelligence (AI) will lead to a development where the first prototype of a self-operating robot may not be far away.

The ERAS protocol has to continuously adapt to this development. However, despite the growing evidence of the benefits of ERAS programs, adoption of evidence-based care in surgical units has been slow. Traditional perioperative care prevails in most centers, sometimes modified by a few selected components of the ERAS protocol aiming to reach the same postoperative outcome but with less effort.

However, things are constantly improving. More and more colorectal centers are seeing the benefits of proper ERAS implementation and recognizing the value of access to solid data that enables not only improvements in local perioperative care and benchmarking with other centers but also a unique environment to investigate new surgical techniques and new treatment modalities.

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Enhanced Recovery After Surgery: Recommendations for Esophagectomy

41

Piers R. Boshier, Fredrik Klevebro, and Donald E. Low

Introduction

Surgical resection of the esophagus for malignant and benign disease remains a formidable challenge. The historical association of esophagectomy with elevated rates of perioperative morbidity and mortality—considered a distinguishing feature among oncological procedures—is frequently ascribed to the technical complexity of this operation and the physiological stress incurred by patients at multiple points of the treatment pathway.

Due to these challenges, there has been a recognition of the importance of a standardized approach to the management of patients requiring esophageal resection [1, 2]. In the case of complex operations such as esophagectomy where there are numerous opportunities to intervene during the course of patient care, the accrual of sequential marginal gains can be combined to achieve significant improvements in overall outcomes.

For any standardized pathway to impact upon outcomes, it must consistently emphasize the importance of the multidisciplinary team, including the patient and their social support network, in all aspects of care. All members of the multidisciplinary team engaged in the care of esophagectomy patients must be in agreement regarding any proposed changes to patient care pathways and demonstrate a collective commitment to their sustained implementation.

A number of centers have established standardized care pathways for the management of patients undergoing esophagectomy. These pathways have drawn from other examples within surgical oncology. Variation in the design and implementation of such pathways within different institutions continues to be a limiting factor when seeking to derive summative evidence for wider application. Notwithstanding, there have been reports that standardization of care can be associated with improvement in important outcomes in patients undergoing esophagectomy, including anastomotic leak rate and length of hospital stay [1]. Recognizing the importance of consolidating ERAS principles in esophagectomy, the ERAS® Society has recently published guidelines for perioperative care [3]. These guidelines, developed by a multidisciplinary working group of international experts, constitute an important point of reference for standardized care in esophagectomy patients. Critically, these recommendations address those aspects of care unique to this high-risk population.

In this review, we will discuss the core elements of an enhanced recovery program for esophagectomy that are applicable to both malignant and benign disease (Fig. 41.1). While this review is divided between pre-, intra-, and postoperative interventions, in reality ERAS principles should be seen as a continuum and not as isolated events.

Preoperative Components

Multidisciplinary Tumor Board

While the benefits of the multidisciplinary tumor board in regard to postoperative outcomes and survival have yet to be unequivocally established, they have become an important component of patient care in many centers. A number of studies have suggested that patients whose care is subject to formal multidisciplinary review routinely receive better coordinated treatment that is more closely aligned with evidence for best practice [4]. More accurate cancer staging, and its impact on treatment selection within a multidisciplinary tumor board, has been linked to better patient outcomes after esophagectomy [5, 6]. Some studies have

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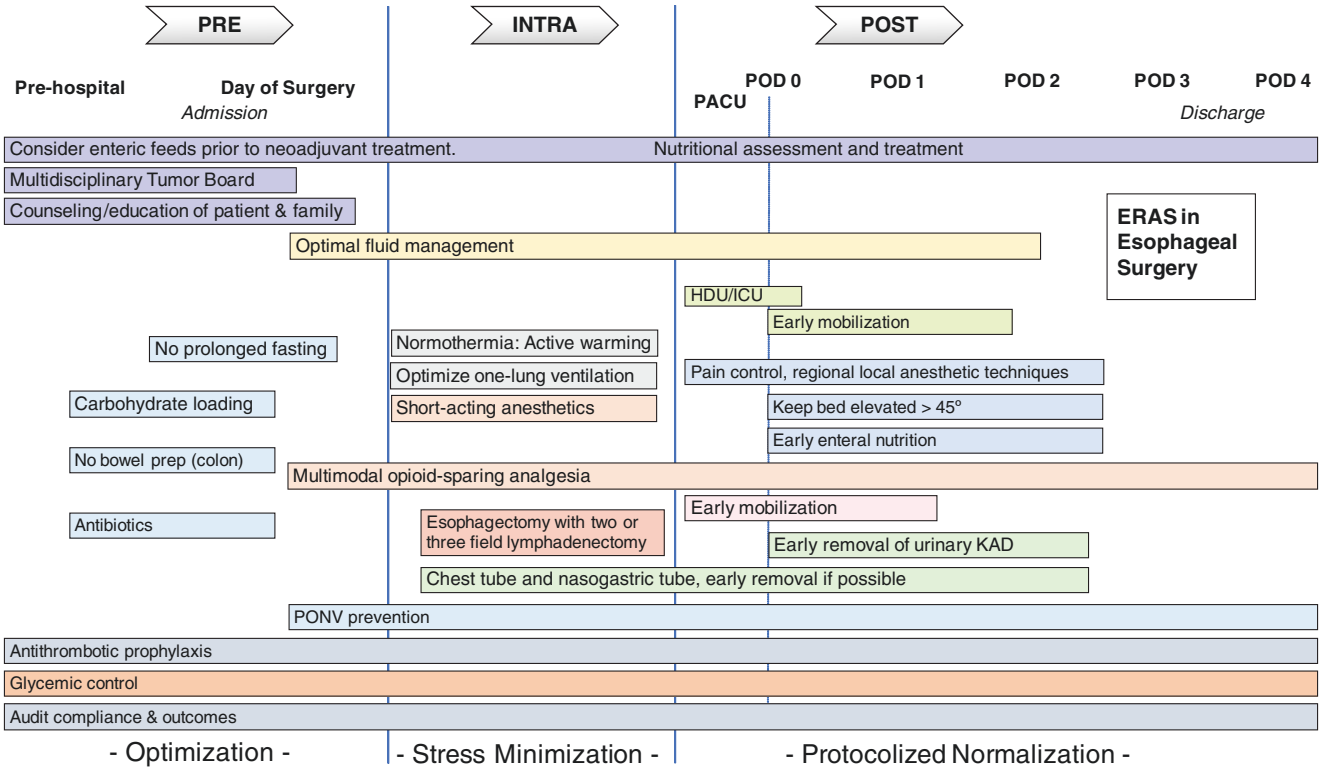

Fig. 41.1 General ERAS principles for esophageal surgery. PACU postanesthesia care unit, HDU high-dependency unit, ICU intensive care unit, KAD indwelling urinary catheter, PONV postoperative nausea and vomiting

shown that presentation at a tumor board can play a significant role in determining a patient's final care plan [7].

In addition to oncological considerations, other important determinants of patient care—including comorbidity, physiological reserve, and nutrition—often feature as components of tumor board discussions. The tumor board should selectively seek engagement from a number of members of the multidisciplinary team, including the patient who should remain the central focus and be kept informed of recommendations. The needs of patient populations who do not traditionally receive the benefit of formal multidisciplinary discussion, such as those with benign or emergency indications of for esophagectomy, should not be forgotten. Implementation of recommendations from the multidisciplinary team should also be monitored to ensure compliance with best practice recommendations [7].

Prehabilitation

Esophagectomy for cancer has an increased risk of physiological debilitation due to multimodal therapy. Preoperative frailty reflects a complex syndrome of age- and disease-related deficits, which together contribute to a greater risk of adverse health outcomes [8, 9]. Such outcomes are characteristic of a lack of resilience to physiological stressors. It follows that frailty has been linked to higher rates of postoperative morbidity, mortality, and utilization of healthcare resources [10–13]. As a highly invasive surgical procedure, esophagectomy imposes a significant physiological burden upon patients. It is anticipated that efforts to build resilience prior to surgery are best provided within a structured prehabilitation program (see also Chap. 10).

Table 41.1 Proposed components of a prehabilitation program for esophagectomy

Domain	Intervention
Nutrition	Dietary advice Protein supplementation Consideration for feeding adjuncts
Physical performance	Exercise program incorporating: Aerobic training Strength training
Medical comorbidities	Optimization of: Glycemic control Blood pressure
Risk behaviors	Smoking cessation Alcohol reduction
Psychological health	Treatment of depression Reducing emotions stress Building mental resilience

Proposed components of a prehabilitation program are outlined in Table 41.1 and broadly include interventions to address nutrition, physical performance, medical comorbidities, risk behaviors, and psychological health. While interventions should be developed within a structured and

goal-directed framework, they should be personalized, where possible, for individual patient needs.

A number of randomized clinical trials and observational studies have shown a benefit for prehabilitation in regard to improvement in postoperative physical function [14–18], although evidence for an improvement in clinical outcomes is less clear. One recent meta-analysis of studies involving patients undergoing colorectal surgery determined that nutritional prehabilitation, with or without an associated exercise program, significantly reduced length of hospital stay [19].

It is recognized that patient engagement and compliance with prehabilitation programs is variable. The extent and method of supervision, as well as the choice between hospital- and home-based programs, should therefore be carefully considered as these factors may affect patient compliance.

Until the findings of several ongoing trials are known, there remains limited evidence concerning the efficacy of prehabilitation programs in patients undergoing esophagectomy. In the interim, drawing from other surgical disciplines, it may be presupposed that this intervention could have an important position in the future care of such patients. Considering the increased application of early mobilization following esophagectomy, all patients should be encouraged to initiate an age and physiologically appropriate aerobic exercise program prior to surgery.

Nutrition

Rates of malnutrition in esophageal cancer patients are among the highest of any malignancy [20, 21] and are predictive of worse perioperative and long-term outcomes [22]. In esophageal cancer, as in other solid tumors, the inability to maintain adequate nutritional intake typically reflects some degree of anorexia in addition to an underlying alteration in metabolic and inflammatory pathways [21, 23]. Malnutrition may also be a consequence of pathological esophageal obstruction and the combined effects of multimodal therapeutic intervention with neoadjuvant chemotherapy and chemoradiotherapy.

Assessment of nutritional status should occur in all patients planning to undergo esophagectomy at the earliest opportunity—ideally by a qualified dietician. Assessment should include the acquisition of baseline anthropometric measurements but, more importantly, a suitable dietary history that includes recent weight loss. Identification of patients who might be at particularly high risk of adverse outcome as a result of malnutrition may be aided by the use of established guidelines such as those published by the European Society for Clinical Nutrition and Metabolism (ESPEN) [24]. There is emerging evidence that the assessment of body composition, using routine computed tomography (CT) images, could provide additional information regarding a patient's nutritional status and risk of adverse surgical outcomes [22].

In patients who are considered to be at low risk of malnutrition—defined by minimal weight loss and preservation of normal oral intake—simple dietary advice may suffice. For other patients with risk factors for moderate malnutrition—including 5–9% unintentional weight loss and/or mild to moderate dysphagia—protein and energy supplementation is advised. Patients at high risk of malnutrition, >10% unintentional weight loss, severe dysphagia, and/or low body mass index (BMI) (<18.5 Kg/m^2), should be considered for nutritional support—preferably enteral by tube feeding, or if this is not available, parenteral nutrition [3]. In esophageal cancer patients who are awaiting surgery, implementation of preoperative nutritional support preserves weight and decreases severe postoperative complications [25].

Operative Components

Timing of Surgery

In determining the optimal timing of esophagectomy, a balance must often be found between the desires to expedite definitive surgery before tumor progression and the opposing need to allow for pathological downstaging and recovery after neoadjuvant therapy. As previously mentioned, the period before surgery is also an important opportunity to build patient fortitude.

Neoadjuvant therapy prior to esophagectomy is now routinely given to patients with stage II or III esophageal cancer. For patients receiving neoadjuvant chemoradiotherapy, the competing pressures of allowing adequate time to recover from therapeutic toxicities in the presence of ongoing tumor regressive effects versus the risk of new tumor progression and evolving fibrosis of surgical tissue plane must be carefully balanced. Based on evidence derived from randomized trials and meta-analysis, an interval of 6–10 weeks has been proposed as the optimum time of surgery after neoadjuvant chemoradiotherapy [3]. In the case of neoadjuvant chemotherapy, the recommended interval before esophagectomy is 6 weeks and is based on historical evidence derived from relevant clinical trials within the field [26, 27].

Surgical Access

In the last 25 years, there has been an increase in the number of esophagectomies performed via minimally invasive and hybrid techniques. Contemporary data from 24 high-volume centers in 14 countries indicate that 48% of esophagectomies were performed via a minimally invasive approach [28]. However, questions still remain regarding the optimal surgical approach for esophagectomy.

There have been 11 meta-analyses comparing the outcomes of open versus minimally invasive esophagectomy

[29–39]. Taken together, their findings suggest the minimally invasive techniques are associated with significantly lower perioperative blood loss [29, 31, 33, 34, 37], overall postoperative morbidity [29, 31, 34, 35, 37], pulmonary complications [29, 31, 33, 34, 36–38], early mortality [29, 37, 38], and length of hospital stay [29, 34, 36, 37]. Minimally invasive procedures were more often associated with longer operative time but equivalent lymph node harvest [33, 36, 37]. Overall survival was either equivalent [30, 31] or superior [33] in the minimally invasive cohort. Results of both the TIME (traditional invasive vs. minimally invasive esophagectomy) and MIRO (minimally invasive surgery for esophageal cancer) trials, respectively, showed that totally minimally invasive and hybrid minimally invasive esophagectomy are associated with lower postoperative morbidity and equivalent survival at 3 years [40–43]. The ongoing Japan Clinical Oncology Group (JCOG1409) trial is expected to further determine the benefits of minimally invasive esophagectomy.

Lymphadenectomy

Esophageal cancers frequently metastasize early to locoregional lymph nodes aided by dense submucosal lymphatics. Local lymph nodes may be involved in one in five patients with submucosal tumor extension (T1) increasing to three in five in cases where the tumor has invaded the muscle of the esophageal wall (T2) [44]. There is evidence that radical lymphadenectomy reduces local recurrences rates and improves long-term survival as well as supporting more accurate pathological staging [45–48]. Proponents of a more conservative approach would contend that radical lymphadenectomy increases morbidity in the absence of conclusive evidence of improved survival. It is currently recommended that the extent of the lymphadenectomy performed during esophagectomy should reflect both the stage of the tumor and its position within the esophagus [45–47, 49].

Esophageal Reconstruction

Reconstruction of the esophagus is most commonly achieved through tubularization of the remnant stomach, primarily because of its accessibility and the requirement for a single anastomosis. Where there is significant tumor invasion of the proximal stomach or previous history of gastric resection, colon or jejunum can be used to form the conduit. In the majority of cases, it is preferential for the conduit to follow the native route of the esophagus within the posterior mediastinum. Selection of an alternative conduit route may, however, be necessary when previous surgery or active infection precludes access through the posterior mediastinum. Two meta-analyses of studies comparing anastomotic technique determined that linearly stapled (hybrid) [50] but not circular stapled [51] anastomotic techniques were superior to hand-sewn anastomoses.

Surgical Drain, Nasogastric Tube, and Urinary Catheter Placement

Placement of surgical drains during esophagectomy occurs largely in the absence of evidence-based guidelines. Although drains likely aid detection and management of anastomotic and chyle leaks in addition to other clinically significant fluid collections, they may be associated with pain and reduced mobility [52].

Placement of a perianastomotic drain within either the thoracic cavity or neck has not been shown to influence leak rate. In one large retrospective study, thoracic anastomotic drainage did aid in the earlier detection and faster resolution of leaks but without the requirement for additional invasive intervention [53]. Likewise, cervical anastomotic drains are typically removed before a clinically significant leak becomes apparent and therefore have questionable clinical benefit [54].

Current evidence derived from studies in both esophageal and pulmonary surgery would appear to support placement of a single centrally placed chest drain left on passive drainage that can be subsequently removed in the absence of obvious leakage of air or chyle. One recent study has offered evidence that minimally invasive esophagectomy without chest drain placement is associated with greater patient satisfaction but no increased postoperative morbidity [55].

Elimination of nasogastric tubes following gastrointestinal surgery has been a common feature of ERAS programs. After esophagectomy, their use is traditionally believed to benefit conduit decompression preventing aspiration and anastomotic leak. Removal of the nasogastric tube as early as postoperative day 2 after esophagectomy was not, however, associated with worse outcomes in one study [56]. Current recommendations are that nasogastric tubes should be targeted for early removal in appropriate patients.

The placement of a Foley catheter at the time of esophagectomy is widely considered standard practice. While early removal of a urinary catheter has been shown to reduce rates of urinary tract infection, in patients who have undergone thoracotomy with an epidural catheter in situ, there is a significant risk of subsequent urinary retention necessitating catheter reinsertion, especially in males [3]. A clearly defined and agreed protocol for bladder assessment with criteria for catheter reinsertion should therefore be in place when considering early (<48 hours) removal of urinary catheters within an ERAS program for esophagectomy. Use of a suprapubic catheter may be considered in circumstances where insertion is likely to exceed 4 days, as their use is associated with lower infection rates and greater

patient satisfaction as determined by meta-analysis of studies in patients following abdominal surgery [57].

Post-Esophagectomy Nutrition

Concern regarding the risk of aspiration and anastomotic leak has historically delayed oral feeding after esophagectomy. In order, therefore, to avoid further nutritional deterioration during the early postoperative period, an appropriate plan for establishing feeding should be considered in all patients, preferably prior to surgery. Several randomized controlled trials have compared total parenteral nutrition and enteral tube feeding and determined equivalence in the number of central venous catheter and enteral feeding tube complications. One study did observe a higher rate of potentially life-threatening complications in patients who received total parenteral nutrition [58]. Reduction of the surgical stress response and preservation of gut barrier and immunological function are further benefits of enteral feeding.

A number of studies have examined the feasibility and safety of early oral feeding after esophagectomy. When compared to patients whose oral intake was delayed until postoperative day 5 following esophagectomy, early oral feeding on postoperative day 1 was not associated with higher rates of complications, including anastomotic leak and pneumonia [59, 60]. Intensive care unit and hospital stay were significantly shorter in patients who received early oral feeding, but median caloric intake was 58% of what was required on postoperative day 5 [61].

Current recommendations support the use of either a percutaneous feeding jejunostomy or a nasojejunal/nasoduodenal tube for the provision of early enteral nutrition after esophagectomy [3]. Once a route for providing enteral nutrition has been established, it is recommended that full caloric requirements be reached by postoperative days 3–6 [60]. There is no clear evidence supporting the use of pharmaconutrition over traditional enteral feeding solutions, as their use is not currently recommended [3]. Further studies are also needed to clarify the safety and efficacy of early oral feeding after esophagectomy.

Anesthetic Management

Anesthetic management during esophagectomy should form a core component of any ERAS program with the intention of minimizing intraoperative cardiorespiratory stress and achieving safe early extubation [3].

Although the choice of specific anesthetic agents has not been shown to influence outcomes in patients undergoing esophagectomy, monitoring depth of anesthesia using bispectral index [62] and use of short- or intermediate-acting neuromuscular blockers may facilitate early extubation [63].

The ventilatory strategy for esophagectomy is made more complex by the frequent requirement for periods of one-lung ventilation. In the case of two-lung ventilation, there is good evidence to support the use of lung protective ventilation with tidal volumes of 6–8 ml/Kg predicted body weight. While evidence for the routine use of positive end-expiratory pressure (2–5 cmH_2O) and recruitment maneuvers is limited, there is emerging appreciation for the importance of maintaining low driving pressures for the prevention of lung injury [64]. One-lung ventilation poses its own specific challenges. Efforts to maintain oxygenation and avoid hypercapnia may result in overventilation and delivery of excessive concentrations of oxygen to the dependent lung. Optimization of lung perfusion endeavors to balance the risk of both shunting of blood and the effects of hypoxic pulmonary vasoconstriction that may worsen ischemia and inevitable reperfusion injury that occurs in the collapsed lung. One randomized controlled trial demonstrated that during one-lung ventilation, tidal volumes of 5 ml/Kg and positive end-expiratory pressure of 5 cmH_2O compared to non-protective ventilatory strategy (tidal volume 9 ml/Kg through surgery) reduced the systemic inflammatory response to surgery while improving lung function and earlier extubation [65]. The concentration of inspired oxygen should also be minimized with the aim of maintaining oxygen saturations of >92%. Mild permissive hypercapnia can be accepted at the expense of higher tidal volumes and respiratory rates. Hypoxia (SpO_2 persistently <90%) may be rectified by increased positive end-expiratory pressure used for intermittent recruitment maneuvers in the ventilated lung or, if necessary, temporary reinflation of the collapsed lung. The duration of one-lung ventilation should be minimized where possible.

Excessive intra- and postoperative fluid administration should be avoided due to its association with tissue edema and adverse cardiovascular and gastrointestinal function. A balanced fluid regimen is recommended with the aim of restricting weight gain to <2 kg/day. Strategies including goal-direct and balanced fluid therapy may also provide clinical benefit. The practice of goal-direct therapy is one where fluid administration is optimized according to cardiac output and other objective hemodynamic parameters. Taniguchi et al. recently reported that, compared to a historical patient cohort, the introduction of goal-direct therapy within a defined ERAS program in esophagectomy patients enhances postoperative gastrointestinal function and mobilization, although without impacting length of stay or complications [66]. Meta-analysis of nine randomized controlled trials of intravenous fluid therapy in major elective abdominal surgery reclassified patients according to whether they received balanced or imbalanced therapy [67]. In this study, patients who were managed in a state of "fluid balance" had significantly fewer complications and shorter hospital stay compared to patients who were either under- or over-hydrated. Current recommendations are therefore for balanced fluid therapy with minimal weight gain and the use of crystalloids

solution as opposed to 0.9% saline and colloids [68, 69]. Use of vasopressors may be needed in circumstances of hypotensive normovolemia—a common consequence of epidural analgesia. As a general rule, mean arterial pressures of 70 mm Hg and urine output >0.5 ml/Kg/hr. should be targeted, although lower urine outputs may be tolerated in patients without risk factors for acute kidney injury [70]. In the normovolemic patient, vasopressors can be utilized to increase mean arterial pressure [71].

Postoperative Components

Analgesia

The requirement for both abdominal and thoracic access makes pain control after esophagectomy within enhanced recovery programs a more complex issue [72]. Adequate pain control is critical to the prevention of postoperative morbidity [73]. A multimodal approach to the provision of analgesia is generally favored, encompassing local and regional anesthetic techniques while minimizing opioid usage.

While routinely performed in patients undergoing major elective surgeries, insertion of an epidural catheter is vulnerable to procedural and patient-specific factors that can lead to uncertainty regarding catheter placement. Accordingly the rate of "failure" of epidural analgesia is reported to vary in the range of 14–43% [74–78]. Use of epidurography in selective patients may help to avoid uncertainty regarding epidural catheter placement expediting clinical decision-making [74]. In patients with correctly sited epidural catheters, avoidance of bolusing and infusion of dilute local anesthetic and opioid solution may help prevent unwanted motor and sympathetic blockade. A multimodal pain management team should evaluate the treatment on a daily basis after surgery. A firsthand choice for pain management is to ensure the epidural catheter placement and optimize the dose of diluted local anesthetics and opioids. Acetaminophen should be administered every 6 hours. Nonsteroidal anti-inflammatory drugs (NSAIDs) can be used in patients without renal failure and after individual assessment. The aim with this strategy is to minimize the use of postoperative oral or parenteral opioids.

Use of paravertebral nerve blocks offers an effective alternative to epidural analgesia. Advantages of this approach include the ability to place blocks under direct supervision and the avoidance of some of the side effects of epidural analgesia [79–81].

Mobilization

Ideally mobilization of patients after esophagectomy should occur within an established framework that can be adapted to individual patient needs. As previously discussed, prehabilitation has a role in preparing patients physically for surgery as well as setting expectations for postoperative care. Patient mobilization should ideally occur on the day of surgery and continue in an incremental fashion until a predefined goal (preferably independent mobilization), which has been agreed to by the patient, is achieved. Challenges to achieving this may include delayed extubation, inadequate analgesia, postoperative complications, and hemodynamic instability, each of which can be countered by organizational readiness and adherence to many of the recommendations already discussed. At least in the initial postoperative period after esophagectomy, patient mobilization should be overseen by physical and occupational therapists but ultimately supervised by nursing and other allied healthcare personnel. All members of the patient care team, including the patient and their family, should be aware of mobilization targets, and their potential benefits, and be invested and engaged in the process of postoperative mobilization. It should not be forgotten that mobilization is one of the few processes that can be "owned" by the patient and their family and can serve as an important source of empowerment.

Preoperative Components

Pharmacological Prophylaxis

The use of pharmacological agents to mitigate the risk of common complications should be considered in all patients who are undergoing esophagectomy. Typically such regimens should acknowledge the importance of preventing thromboembolic events, postoperative nausea and vomiting, and surgical site infection.

Antithrombotic Prophylaxis

Antithrombotic prophylaxis with low-molecular-weight heparin is recommended to be administered 2–12 hours before start of surgery and continued at least 4 weeks postoperatively.

Postoperative Nausea and Vomiting (PONV) Prophylaxis

Prophylaxis should be considered for all high-risk patients. If PONV occurs, treatment with 5-hydroxytryptamine receptor antagonists is preferred.

Antimicrobial Prophylaxis

Antibiotic prophylaxis is recommended to reduce the risk for postoperative surgical site infections. Appropriate parenteral or oral antimicrobial should be administered in a correct dose for each patient. There is no evidence to support prolonged antimicrobial prophylaxis.

Preoperative Fasting

Preoperative fasting over 8 hours should be avoided, and clear liquids, including specific high-carbohydrate drinks, should be allowed up to 2 hours before surgery. Patients with significant dysphagia should receive enteral or parenteral preoperative nutrition.

Audit

The ERAS® Society has placed specific emphasis on the conduct of continuous institutional audit as a means of reviewing outcomes and the practice of guideline elements. Individual institutions must first seek to understand their own practices and outcomes in order to provide a reliable benchmark against which to assess the impact of changes to the patient care pathway. Audit should be used to regularly monitor adherence to guidelines, as improved compliance has been associated with reduced morbidity and length of hospital stay and long-term cancer survival [82–86]. The opportunity to contribute institutional data to regional, national, and/or international datasets should be embraced as a method in forming standards of practice within a wider context.

Conclusion

Even in high-volume expert centers, as many as two out of every three patients will suffer a complication after esophagectomy, with a documented 90-day mortality in high-volume expert centers of 4.5% [28]. In an effort to counter the high morbidity and mortality that is associated with esophagectomy, many institutions have initiated ERAS programs to support standardized care in this patient group. The nature and complexity of esophageal surgery has, however, meant that a strong evidence basis for many current recommendations is either yet to be established or borrowed from other fields of surgery. The recently published guidelines for perioperative care in esophagectomy developed by the ERAS society will, nevertheless, serve as a reference point (Table 41.2) [3].

Table 41.2 Components of the ERAS program for esophagectomy

ERAS component	Recommendation	Level	Grade
Multidisciplinary tumor board	Applied in every patient	Moderate	Strong
Prehabilitation	Patients may benefit from prehabilitation programs	Low	Moderate
Preoperative nutrition treatment	Important to assess and when indicated treat nutritional deficiency in all patients	Low	Strong
Timing of surgery	After neoadjuvant chemotherapy 3–6 weeks. After neoadjuvant chemoradiotherapy 6–10 weeks	Moderate	Moderate
Surgical access	Open or minimally invasive techniques are recommended	Moderate	Moderate
Lymphadenectomy	Two-field lymphadenectomy for AC in the middle and lower third of the esophagus. Three-field is recommended in upper third SCC performed at high-volume units	Moderate	Strong
Esophageal reconstruction	Gastric conduit in first hand, colon and jejunum are second option	Low/ moderate	Strong
Surgical drain	Avoid cervical drain, chest drain is recommended but should be removed in the absence of air and chyle leaks	Moderate	Strong
Nasogastric tube	Recommended with early removal (day 2) when clinically appropriate	Moderate	Strong
Urinary catheter	Recommended during epidural pain treatment	High	Strong
Post-esophagectomy nutrition	Early enteral nutrition is recommended	Moderate	Strong
Anesthetic management	Use volatile or intravenous anesthetics. Avoid fluid overload. Apply lung protective strategies	Moderate	Strong
Postoperative analgesia	Epidural with local anesthetics and opioids, in combination with regular acetaminophen. NSAIDs can be used in nonrenal failure patients if clinically appropriate	Moderate	Strong
Postoperative mobilization	Early mobilization is recommended	Moderate	Strong
Antithrombotic prophylaxis	Recommended with low-molecular-weight heparin from 12 to 2 hours before surgery until 4 weeks postoperatively	High	Strong
PONV	Prophylaxis to high-risk patients	Low	Strong
Antimicrobial prophylaxis	Recommended. Prolonged prophylaxis should be avoided	High	Strong
Preoperative fasting	Recommended for solid food 8 hours and for drinks 2 hours preoperatively	High	Strong

NSAIDs nonsteroidal anti-inflammatory drugs, *PONV* postoperative nausea and vomiting, *AC* adenocarcinoma, *SCC* squamous cell carcinoma

Greater use of chemoradiotherapy in the management of esophageal cancer is challenging the role of surgery as the only "definitive" treatment modality. For surgery to retain its status, more must be done to improve both its safety and efficacy. It is through the wider adoption of ERAS principals and incremental marginal gains in the care of esophagectomy patients that such goals can be achieved.

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Enhanced Recovery After Gastrectomy

42

Kim Erlend Mortensen

Introduction and Methods

Although several publications have highlighted sporadic efforts to evaluate enhanced recovery or fast-track pathways for patients undergoing elective gastrectomy for cancer [1, 2], comprehensive and evidence-based frameworks are few. A large body of literature suggests that such protocols are pivotal in improving patient outcomes. This chapter is based upon work from an international working group with extensive experience in enhanced recovery within the ERAS® Society to achieve a broad knowledge base and ensure international validity for the conclusions. A core group involved in the original *British Journal of Surgery* publication performed a comprehensive literature search and constructed a primary set of recommendations based on reports published between 1985 and 2013. The entire authorship group repeatedly added scientific content and adjusted evaluation of evidence and strength of conclusions. For this book chapter, an updated literature search was performed during the spring of 2018.

Emphasis was placed on publications and papers of good quality: moderate- and high-quality randomized clinical trials (RCTs) and large, high-quality cohort studies, as well as systematic reviews and meta-analyses of these. Retrospective series were included if data of better quality were lacking.

The author group specifically included only literature on elective gastric cancer surgery. This was because of the large differences in the extent of dissection necessary in oncological surgery compared with surgery for benign disease (such as bariatric surgery)—the consequences of which are very different postoperative courses for these patients and so varying needs for perioperative treatment guidelines. Emergency surgery of any kind is not included.

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Quality Assessment and Grading

Level of evidence and recommendations were set according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system [3–6]. Recommendations were based not only on the quality of evidence (high, moderate, low, very low) but also on the balance between wanted and unwanted effects and on values and preferences. The latter implies that, in some instances, strong recommendations may be reached from low-quality data and vice versa.

Procedure-Specific Items Versus General Upper Abdominal Surgery Items

Several enhanced recovery items are probably unrelated to the specific intra-abdominal procedure, and these are referred to here as "general" as opposed to "procedure-specific" items. A recent publication has assessed [7] a large number of general enhanced recovery care items and reached a consensus on perioperative care recommendations for patients undergoing pancreaticoduodenectomy. In the absence of procedure-specific evidence, some of these updated recommendations are considered to be valid also for patients undergoing elective gastrectomy (Fig. 42.1). These items are presented in part 2 of the results.

Results Part 1: Procedure-Specific Items

A summary of the procedure-specific items is shown in Table 42.1.

Preoperative Nutrition

A uniform definition of malnutrition that identifies those who will benefit from preoperative nutrition is suggested in

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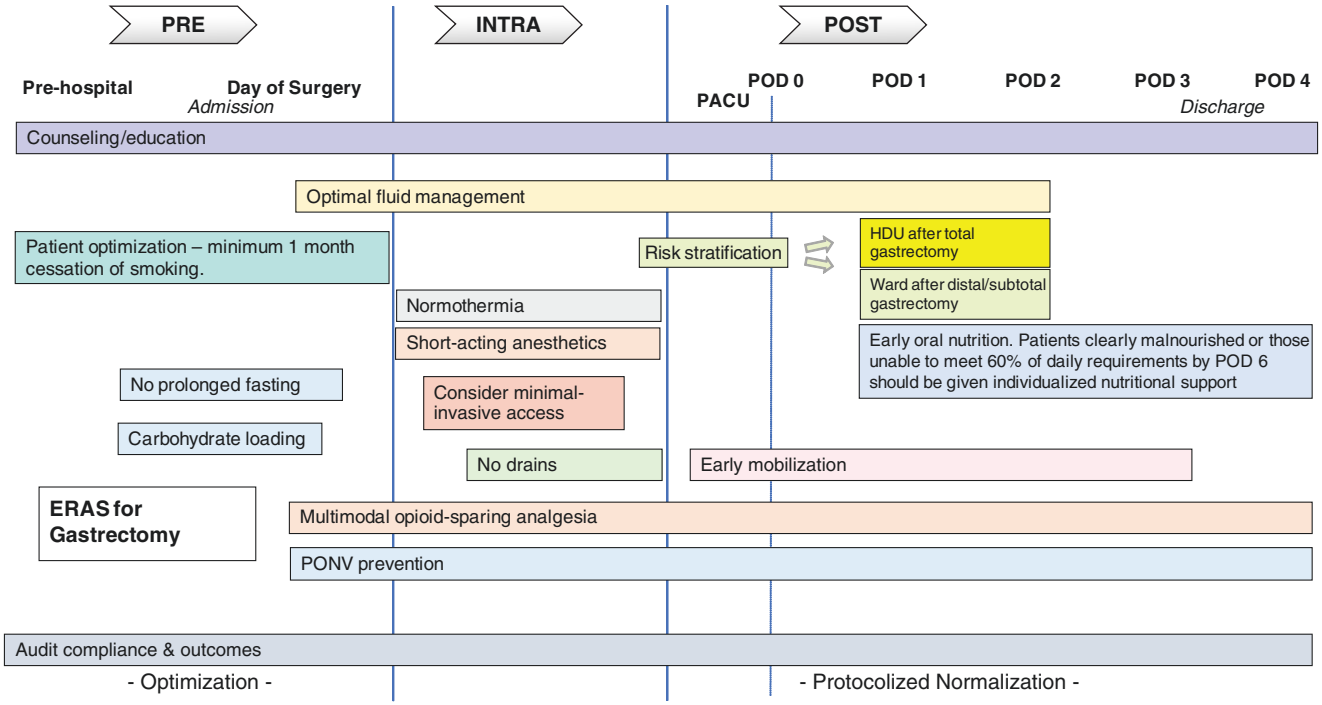

Fig. 42.1 General ERAS principles for gastrectomy. PACU post anesthesia care unit, HDU high-dependency unit, PONV postoperative nausea and vomiting

Table 42.1 Procedure-specific guidelines for perioperative care for gastrectomy: ERAS® Society recommendations

	Summary and recommendations	Evidence level	Recommendation grade
Preoperative nutrition	Routine use of preoperative artificial nutrition is not warranted, but significantly malnourished patients should be optimized with oral supplements or enteral nutrition before surgery	Very low	Strong
Preoperative oral pharmaconutrition	The benefit shown for major gastrointestinal cancer surgery in general has not been reproduced in dedicated trials on patients undergoing gastrectomy. Although a benefit cannot be excluded, there is presently insufficient evidence for this patient group	Moderate	Weak
Access	*Distal gastrectomy:* Evidence supports LADG in early gastric cancer as it results in fewer complications, faster recovery and may be performed to a standard that is oncologically equivalent to open access surgery	High	Strong
	For advanced disease, T2–T4a gastric cancer, more data on long-term survival comparing LADG and ODG are needed	Moderate	Weak
	Total gastrectomy: There is some evidence supporting LATG owing to lower postoperative complications, shorter hospital stay, and oncological safety however, LATG is technically demanding	Moderate	Weak
Wound catheters and TAP block	Evidence is conflicting regarding wound catheters in abdominal surgery	Wound catheters: low to moderate	Weak
	Evidence is strong in support of TAP block in abdominal surgery in general, although the effect is only evident during the first 48 hours after surgery and none of the evidence is from gastrectomies	TAP blocks: low	Weak
Intravenous analgesia	Several alternative methods for intravenous analgesia exists—most conferring comparable analgesia to traditional EDA and opioids	Moderate	Strong
Nasogastric/nasojejunal decompression	Nasogastric tubes should not be used routinely in the setting of enhanced recovery protocols in gastric surgery	High	Strong
Perianastomotic drains	Avoiding the use of abdominal drains may reduce drain-related complications and shorten hospital stay after gastrectomy	High	Strong
Early postoperative diet and artificial nutrition	Patients undergoing total gastrectomy should be offered drink and food at will from POD 1. They should be advised to begin cautiously and increase intake according to tolerance	Moderate	Weak
	Patients clearly malnourished or those unable to meet 60% of daily requirements by POD 6 should be given individualized nutritional support	Moderate	Strong
Audit	Systematic audit improves compliance and clinical outcomes	Low	Strong

LADG laparoscopically assisted distal gastrectomy, *ODG* open distal gastrectomy, *LATG* laparoscopically assisted total gastrectomy, *TAP* transversus abdominis plane, *EDA* epidural analgesia, *POD* postoperative day

the 2009 European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines [8]. Malnutrition is associated with increased morbidity after surgery [9]. It appears prudent to identify these patients [10] and give enteral sip feeds or nasogastric or nasojejunal tube feeding, although data to support intervention are weak. If the tumor precludes access to the duodenum, parenteral nutrition may be warranted [9]. For patients not suffering from significant malnutrition, preoperative artificial nutrition has not been shown to confer benefits [8].

Routine use of preoperative artificial nutrition is not warranted, but significantly malnourished patients should be optimized with oral supplements or enteral nutrition before surgery.

Preoperative Oral Pharmaconutrition

Pharmaconutrition or immunonutrition (IN), denoting the administration of immune-stimulating nutrients (generally arginine, glutamine, omega-3 fatty acids, and/or nucleotides), has been evaluated extensively in major surgery, and more than 20 RCTs have included patients undergoing upper gastrointestinal surgery [11]. Conclusions are difficult as IN is administered to different patient groups, at different time periods relating to surgery, in different combinations and dosages, and compared with control preparations that are not always isonitrogenous. Many trials are more than 10 years old, few are blinded, and few investigated only a single component. For major abdominal cancer surgery as a group, there appears to be a benefit from perioperative enteral IN with respect to the rate of infectious complications in malnourished patients, but results are inconsistent [11–17]. In a recent double-blind RCT [18], preoperative IN did not show any benefit in patients, of whom two of three underwent major upper gastrointestinal or hepatopancreatobiliary (HPB) cancer surgery, and all were at nutritional risk. A reduction in mortality has never been demonstrated. A meta-analysis [11] in 2011 identified only one double-blinded trial with adequate blinding assessing IN for gastric cancer surgery. In this trial [19], postoperative IN reduced the rate of surgical wound healing complications. Two recent reviews [20, 21] have come to conflicting conclusions regarding IN after esophageal resections, and no benefit was found in a double-blinded RCT [22] in predominantly esophagogastric surgery. In two recent large RCTs [23, 24], IN, given for 5–7 days after operation to patients undergoing gastrectomy or esophagogastrectomy, did not confer any benefit. One recent randomized clinical trial from 2017 compared standard diet with perioperative oral immunonutrition based upon an eicosapentaenoic acid-enriched diet in total gastrectomy for gastric cancer, finding no difference between groups in percentage bodyweight loss at 3 months after surgery [25]. Further trials are warranted, and, as this is an issue that lends itself well to double-blinded RCTs, this should be the study design. Future trials should be conducted in modern perioperative care settings and with single immune-enhancing substances.

The possible benefit of reduced infectious and wound healing complications after major gastrointestinal cancer surgery in general has not been reproduced in dedicated, high-quality trials on patients undergoing gastrectomy. Although a benefit cannot be excluded, there is presently insufficient evidence to support routine administration in this patient group, and its use is not recommended.

Access: Distal Gastrectomy

Distal gastrectomy is defined here as resection of the lower two-thirds of the stomach with lymph node harvest (D1, D1+, and D2) performed according to recommendations from the latest Japanese Gastric Cancer Treatment Guidelines [26]. Early gastric cancer is defined as T1 and any N category and advanced gastric cancer as T2–T4 and any N category.

Six meta-analyses (of 6 RCTs, 8 prospective studies, and 32 retrospective series) compared laparoscopically assisted distal gastrectomy (LADG) with open distal gastrectomy (ODG) [27–32]. Combining these meta-analyses, a total of 4574 patients with largely early gastric cancer treated with LADG and 4260 with ODG were compared. Although three analyses [28–30] reported longer operating times (mean 71 minutes), all reported that laparoscopic access resulted in significantly less blood loss. Three analyses [27, 28, 31] reported shorter time to oral intake (a mean gain of 1 day) and shorter hospital stay (mean 4.5 days less). Overall postoperative morbidity (in particular pulmonary complications) was also reduced after LADG. Two analyses [28–30, 32] reported less postoperative analgesic consumption. There were no differences in anastomotic complications between LADG and ODG. The number of harvested lymph nodes during LADG has been of concern in many publications. Three meta-analyses reported an average of 4.2 fewer lymph nodes harvested [28–30], whereas the other three [27, 31, 32] reported no difference between LADG and ODG. Three RCTs [33–35] including early and advanced gastric cancer reported data on long-term survival (24–62 months), which was found to be similar. Recently a large Korean RCT [36] has showed that LADG for patients with clinical stage I gastric cancer is safe and has a benefit of lower occurrence of wound complications compared with conventional ODG.

Evidence supports LADG in early gastric cancer as it is associated with fewer complications and faster recovery and may be performed to a standard that is oncologically equivalent to open access surgery. For advanced disease, T2–T4

gastric cancer, more data on long-term survival comparing LADG and ODG are needed.

Access: Total Gastrectomy

Three meta-analyses [37–39] compared results from laparoscopically assisted total gastrectomy (LATG) in 1497 patients to open total gastrectomy (OTG) in 1486 patients treated for both early and advanced gastric cancer. All studies reported longer operating times (mean 54 minutes) for LATG, and all three analyses reported that patients treated by a laparoscopic approach had lower blood loss (mean 120 ml less) and shorter hospital stay (mean stay almost 5 days shorter). One analysis [39] reported less postoperative pain, two [37, 39] reported earlier passage of flatus by an average of 1.2 days, one [39] documented fewer postoperative complications (wound infections and ileus), and one [37] found no differences. No meta-analysis reported any difference in number of retrieved lymph nodes between LATG and OTG, and 2 meta-analyses [38, 39] found an equal 60-month recurrence-free survival. Concerns were raised about higher anastomotic leak rates after LATG in another publication [40]. Although the results after laparoscopic distal and total gastrectomies are promising, it must be borne in mind that the evidence level is only moderate owing to the shortage of RCTs and the heterogeneity of data in the prospective and retrospective series on which these trends are based.

Most publications suggest that LATG results in a lower rate of postoperative complications and shorter hospital stay. Data are inconclusive regarding oncological safety for advanced gastric cancer. LATG may be recommended for early gastric cancer wherever surgeons are proficient in the technique and the procedure is established.

Wound Catheters and Transversus Abdominis Plane Block

Wound catheters and transversus abdominis plane (TAP) block offer the potential of incisional analgesia without the need for more invasive methods such as epidural analgesia (EDA). The technique offers an attractive alternative to EDA, as peripheral block of afferent stress-mediating impulses is achieved without troublesome and potentially hazardous hypotension. Furthermore, the risks of complications such as epidural hematomas and abscess formation are avoided. Although there are no specific data regarding gastrectomy, several meta-analyses [41–43] have assessed the efficacy of wound infusion with local anesthetic agents for postoperative analgesia after abdominal surgery in general. One meta-analysis [42], comprising a wide range of surgical procedures, including general surgical laparotomies, showed a significant reduction in postoperative pain, opioid consumption, as well as postoperative nausea and vomiting (PONV). Similarly, in patients undergoing colorectal surgery, there was a reduced use of opioids and reduction in length of hospital stay in patients randomized to preperitoneal wound catheter placement [44]. A more recent meta-analysis [41] did not, however, show any effect of wound infusion with regard to postoperative pain intensity or in opioid consumption after laparotomy. The inconsistency in results may reflect the heterogeneity in techniques used, including catheter placement (subcutaneous, subfascial, preperitoneal), and type, concentration, and dose of local anesthetic. No differences in risk of infectious complications were found between patients in whom a wound catheter was used and those managed without one [41, 43–45].

Several RCTs and meta-analyses [46–49] have suggested a significant reduction in postoperative pain and opioid consumption during the first 24–48 hours after surgery with the use of TAP blocks. There are no studies specifically addressing gastrectomy, and most procedures included in these trials (such as cholecystectomies, appendectomies, and caesarian deliveries) are indeed less invasive, both with regard to abdominal wall incision and extent of internal dissection, than open gastrectomy for cancer [46–49]. Another limitation of TAP blocks in postgastrectomy analgesia is that there is no evidence of an effect exceeding the first 48 hours after operation [46–49]. None of the studies available has suggested an increased risk of infection related to TAP blocks [46–49]. One RCT [50] comparing wound infiltration and patient-controlled analgesia (PCA) using opiates to EDA after open liver resection found that the latter conferred superior analgesia but not faster mobilization or recovery.

Evidence is strong in support of TAP blocks for abdominal surgery in general, although the effect is only evident during the first 48 hours after surgery and none of the evidence is from gastrectomies.

Intravenous Analgesia

One RCT from 2013 with patients undergoing laparoscopic gastrectomy showed a reduction in postoperative fentanyl consumption and pain with preoperative and intraoperative injection of lidocaine by PCA [51]. A double-blinded RCT from 2016 compared oxycodone and sufentanil administration in patient-controlled intravenous analgesia after laparoscopic radical gastrectomy. The overall satisfaction degree was higher in the oxycodone group, while the incidences of side effects were comparable between the two groups [52]. Similar effects benefits were found upon preoperative oxycodone infusion in another RCT published the same year [53]. In an RCT from 2017, 171 patients who

planned open gastrectomy were randomly distributed into one of the three groups: conventional thoracic E-PCA (E-PCA group, $n = 57$), dexmedetomidine in combination with fentanyl-based IV-PCA (dIV-PCA group, $n = 57$), or fentanyl-based IV-PCA only (IV-PCA group, $n = 57$). Dexmedetomidine in combination with fentanyl-based IV-PCA significantly improved postoperative analgesia in patients undergoing open gastrectomy without hemodynamic instability, which was comparable to thoracic E-PCA [54]. Most recently an RCT from 2018 found that intraoperative nefopam administration decreased postoperative pain and opioid consumption in the acute postoperative period after laparoscopic gastrectomy [55].

Several alternative methods for intravenous analgesia exist—most conferring comparable analgesia to traditional EDA and opioids.

Nasogastric/Nasojejunal Decompression

Ten RCTs [1, 56–61] and two meta-analyses [62, 63] have specifically studied nasogastric/nasojejunal tubes in gastrectomies. One RCT [64] not included in the published meta-analyses showed results compatible with those from the RCTs and meta-analyses. A Cochrane review [65] evaluated nasogastric/nasojejunal tubes after several types of operation with a subgroup analysis dedicated to "gastroduodenal operations."

There is strong evidence against the routine use of nasogastric/nasojejunal decompression following gastrectomy. Surgical morbidity was not significantly reduced by decompression [62, 63, 65]. On the contrary, the most recent of the meta-analyses [62] and the Cochrane review [65] concluded that patients without routine decompression experienced significantly fewer pulmonary complications, earlier time to passage of flatus, earlier time to oral diet, and shorter hospital stay. This was not confirmed in another meta-analysis [63].

Nasogastric/nasojejunal tubes should not be used routinely in the setting of enhanced recovery protocols in gastric surgery.

Perianastomotic Drains

Two RCTs [66, 67] including a total of 278 patients treated by subtotal gastrectomy with D1 or D2 lymphadenectomy found no difference in postoperative course in terms of time to passage of flatus, intake of soft diet, or length of hospital stay between patients in whom drains were or were not used. Postoperative complication rates at 30 days were also similar. Another RCT [68] with 60 patients undergoing D2 gastrectomy found that the group with drains experienced longer hospital stays, higher postoperative morbidity with more frequent reoperations, and longer time to oral intake.

A meta-analysis of 4 RCTs [69] including 438 patients randomized to either perianastomotic drain or no drain found no differences between the groups in respect to wound infection, postoperative pulmonary infection, intra-abdominal abscess, mortality, time to flatus, and initiation of soft diet. Both incidence of postoperative complications and length of stay were lower in the no-drain group. A Cochrane analysis in 2011 [70] concluded that there was no convincing evidence to support routine use of postoperative drains after gastrectomy for gastric cancer. This was reiterated in a new Cochrane review published in 2015 [71].

Avoiding the use of abdominal drains may reduce drain-related complications and shorten hospital stay after gastrectomy.

Early Postoperative Diet and Artificial Nutrition

Patients subjected to total gastrectomy are probably at greater risk of malnutrition and cachexia at the time of surgery than other groups of patients with abdominal cancer [20]. This may result both from the location of their tumors but also following neoadjuvant chemotherapy in a large proportion of the patients. A nil-by-mouth regimen for several days after surgery has traditionally been used for these patients [72]. Most trials challenging the ubiquitous nil-by-mouth routine have done so in the setting of distal gastrectomy [73, 74] or, only partly, introducing light food on postoperative day (POD) 1 [21, 75, 76]. Data from Western centers are scant. A large Norwegian multicenter trial [77] randomized patients undergoing major upper gastrointestinal and HPB surgery to food at will from POD 1. Of 447 patients included, 77 had undergone total gastrectomy, and a significant reduction in the number of intra-abdominal abscesses was demonstrated for those allowed food at will in this subgroup. Importantly, no trial has reported any adverse outcome from any attempt at introducing patient-controlled or early introduction of food for patients undergoing gastrectomy.

It may be assumed that total calorie intake is low for the first few days and that some patients will need additional sip feeds or artificial tube or catheter feeding. A recent educational review [20] on nutritional care for patients undergoing esophagus and gastric surgery recommends nutritional support after operation in patients who have not reached the percent of desired intake by the first week following surgery. Nutritional support should preferably be by high-energy oral sip feeds. Enteral tube feeding is indicated where oral intake is not possible, and parenteral nutrition only when the gut is not working or is inaccessible. Although robust data are lacking, it appears pragmatic and safe to provide more intensive

nutritional support both before and after operation to severely malnourished patients.

Patients undergoing total gastrectomy should be offered drink and food at will from POD 1. They should be advised to begin cautiously and increase intake according to tolerance. Patients clearly malnourished or those unable to meet 60% of daily requirements by POD 6 should be given individualized nutritional support, as detailed above.

Audit

Regular audit is crucial to determine clinical outcome and ascertain the implementation and sustained use of a care protocol. There are indications that audit in itself improves clinical results through feedback, and several real-time graphical methods are now available to monitor surgical treatment outcomes of gastroesophageal surgery [78]. It is vital to distinguish between unsuccessful implementation and lack of desired effect from an implemented protocol if results are short of the desired quality standards. Multi-institutional agreement on a common evidence-based treatment platform and joint use of a prospective database is a powerful tool for audit and research.

Systematic audit improves compliance and clinical outcomes.

Results Part 2: General (Not Procedure-Specific) Items

The author group found that the data and recommendations published previously for patients undergoing pancreaticoduodenectomy seem valid for gastrectomy [79]. In the following sections, these recommendations are reiterated and the background for each recommendation addressed briefly. For a fuller consideration of the available literature with expanded references, the reader is referred to the aforementioned publication. A summary of the general items is shown in Table 42.2.

Preoperative Smoking and Alcohol Consumption

Overall postoperative morbidity is increased markedly in alcohol abusers [80], and 4 weeks of abstinence before surgery has been shown to improve outcomes in patients who drank five or more drinks (60 g of ethanol) a day without clinical or historical evidence of alcohol-related illness [81]. Daily smokers have an increased risk of complications [82, 83]. RCTs [83–85] have shown reduced postoperative morbidity after 1 month of smoking cessation. Preoperative physiotherapy reduces postoperative pulmonary complications and length of hospital stay after elective cardiac surgery [86], and preoperative pulmonary rehabilitation before lung cancer surgery decreases postoperative respiratory morbidity and complications [87, 88].

For alcohol abusers, 1 month of abstinence before surgery is beneficial. For daily smokers, 1 month of abstinence before surgery is beneficial. For appropriate groups, both should be attempted. Preoperative pulmonary rehabilitation is advised.

Preoperative Fasting and Preoperative Treatment with Carbohydrates

Fasting from midnight is not supported by evidence [89] and increases insulin resistance and discomfort following abdominal surgery [90, 91]. Guidelines [92] recommend intake of clear fluids up to 2 hours before induction of anesthesia and solids up to 6 hours. A complex clear carbohydrate-rich drink designed for use within 2 hours before anesthesia reduced hunger, thirst, anxiety, and length of stay, as well as postoperative insulin resistance [93–95]. The most recent meta-analysis [96] showed no reduction in in-hospital complication rates. Data on patients having gastrectomy are inadequate, and data for diabetic patients are wanting [97, 98].

Preoperative fasting should be limited to 2 hours for clear fluids and 6 hours for solids. Data extrapolation from studies in major surgery suggests that preoperative oral carbohydrate treatment should be given to patients without diabetes.

Antithrombotic Prophylaxis

A large tumor burden, major surgery, chemotherapy, and prolonged periods of recumbency are risk factors for venous thromboembolism (VTE). Heparins are effective at preventing VTE [99], and fractionated low-molecular-weight heparin (LMWH) has better compliance (once-daily administration) [100]. Injections are usually started 2–12 hours before surgery and continued until the patient is mobilized. Data even support postdischarge treatment for several weeks [101]. Use of LMWH and epidural catheters is controversial [102–105], and a 12-hour interval should probably separate LMWH and catheter insertion and removal. Mechanical measures (intermittent pneumatic leg compression and elastic stockings) may provide additional benefits in patients at increased risk of VTE [106, 107].

LMWH reduces the risk of thromboembolic complications. Administration should probably be continued for 4 weeks after hospital discharge. Concomitant use of EDA

Table 42.2 General (not procedure-specific) enhanced recovery care items as suggested recently for pancreaticoduodenectomy

	Summary and recommendations	Evidence level	Recommendation grade
Preoperative smoking and alcohol consumption	For alcohol abusers, 1 month of abstinence before surgery is beneficial and should be attempted	Alcohol abstention: low	Strong
	For daily smokers, 1 month of abstinence before surgery is beneficial	Smoke cessation: moderate	Strong
	For appropriate groups, both should be attempted		Strong
Preoperative fasting and preoperative treatment with carbohydrates	Intake of clear fluids ≤2 hours before anesthesia does not increase gastric residual volume and is recommended before elective surgery	Fluid intake: high	
	Intake of solids should be withheld 6 hours before anesthesia	Solid intake: low	Fasting: strong
	Data extrapolation from studies in major surgery suggests that preoperative oral carbohydrate treatment should be given to patients without diabetes	Carbohydrate loading: low	Carbohydrate loading: strong
Antithrombotic prophylaxis	LMWH reduces the risk of thromboembolic complications. Concomitant use of epidural analgesia necessitates close adherence to safety guidelines. Mechanical measures should probably be added for patients at high risk	High	Strong
Antimicrobial prophylaxis and skin preparation	Antimicrobial prophylaxis prevents surgical-site infections and should be used in a single-dose manner initiated within 1 hour before skin incision. Repeated intraoperative doses may be necessary depending on the half-life of the drug and duration of procedure	High	Strong
Epidural analgesia	Mid-thoracic epidurals are recommended based on data from studies on major open abdominal surgery showing superior pain relief and fewer respiratory complications compared with use of intravenous opioids	Pain: high Reduced respiratory complications: moderate Overall morbidity: low	Weak
Anesthetic management	Short-acting anesthetic drugs and short-acting muscle relaxants are suggested. Titration of anesthetic agents can be achieved using the BIS	BIS: high	Strong
	Low-tidal-volume ventilation is suggested	Low-tidal-volume ventilation: high	Strong
PONV	Data from the literature on gastrointestinal surgery in patients at risk of PONV show the benefits of using different pharmacological agents depending on the patient's PONV history, type of surgery, and type of anesthesia. Multimodal intervention during and after surgery is indicated	Low	Strong
Avoiding hypothermia	Intraoperative hypothermia should be avoided by using cutaneous warming, i.e., forced-air or circulating-water garment systems	High	Strong
Postoperative glycemic control	Insulin resistance and hyperglycemia are strongly associated with postoperative morbidity and mortality. Treatment of hyperglycemia with intravenous insulin in the ICU improves outcomes, but hypoglycemia remains a risk. Several enhanced recovery protocol items attenuate insulin resistance and facilitate glycemic control without the risk of hypoglycemia. Hyperglycemia should be avoided as far as possible without introducing the risk of hypoglycemia	Low	Strong
Fluid balance	Near-zero fluid balance, avoiding overload of salt and water results in improved outcomes	Fluid balance: high	Strong
	Perioperative monitoring of stroke volume with transesophageal Doppler to optimize cardiac output with fluid boluses may improve outcomes	Esophageal Doppler: moderate	Strong
	Balanced crystalloids should be preferred to 0.9% saline	Balanced crystalloids versus 0.9% saline: Moderate	Strong

In the absence of procedure-specific evidence for these items, the author group considers extrapolation of these recommendations to patients undergoing total gastrectomy to be safe and feasible. For discussion and references, please see original paper

MBP mechanical bowel preparation, *LMWH* low-molecular-weight heparin, *PCA* patient-controlled analgesia, *BIS* bispectral index, *PONV* postoperative nausea and vomiting, *ICU* intensive care unit, *POD* postoperative day

necessitates close adherence to safety guidelines. Mechanical measures should probably be added for patients at high risk.

Antimicrobial Prophylaxis and Skin Preparation

There is sufficient evidence to support the prescription of antimicrobial prophylaxis for major abdominal procedures [108, 109]. Recent studies recommend prescription in a single-dose manner [109], usually advocated within 1 hour before incision; however, recent data suggest that the timing may not be crucial [110]. An extra dose should be given every 3–4 hours during the procedure if drugs with a short half-life are used [111]. The choice of antibiotic varies according to local guidelines but should be different from the drug used for management of established infections. Skin preparation with a scrub of chlorhexidine-alcohol has been claimed to be superior to povidone-iodine in preventing surgical-site infections [112].

Antimicrobial prophylaxis prevents surgical-site infections and should be used in a single-dose manner initiated before skin incision. Repeated intraoperative doses may be necessary depending on the half-life of the drug and duration of the procedure.

Epidural Analgesia

Continuous EDA with or without opioids leads to significantly less postoperative pain than parenteral opioids after open abdominal surgery [113]. A Cochrane review [114] demonstrated that EDA is better than patient-controlled intravenous opioid analgesia in relieving pain 72 hours after open abdominal surgery, and epidural administration of local anesthetic led to a lower rate of ileus after laparotomy than systemic or epidural opioids [115]. EDA was also associated with fewer complications, as well as an improvement in pulmonary function, decreased risk of postoperative pneumonia, better arterial oxygenation after abdominal or thoracic surgery [116], and reduced insulin resistance [117]. Data from a recent RCT [118] indicate that, for patients undergoing gastrectomy for cancer specifically, patient-controlled EDA appears to result in superior pain relief and lower stress response than patient-controlled intravenous analgesia.

Adverse perfusion effects of EDA may be caused by prolonged and extended sympathetic block. This suggests that the beneficial effects of EDA can be preserved provided that the hemodynamic consequences are adequately controlled with vasopressors [119]. Concerns about negative effects on anastomotic healing have been raised after colorectal surgery, but one meta-analysis [120] did not identify differences in rates of anastomotic leakage between patients treated with postoperative local anesthetic epidurals and those receiving systemic or epidural opioids. A potential drawback with EDA is that up to one-third of epidurals may not function adequately [120, 121] possibly owing to catheter misplacement, inadequate dose, or pump failure. For upper abdominal incisions, epidural catheters should be inserted between T5 and T8 root levels. Sensory block should be tested before induction of general anesthesia. EDA should continue for 48 hours and, after a successful stop test, replaced by oral multimodal analgesia. If needed, functioning epidural catheters may be used for a longer duration.

Mid-thoracic epidurals are recommended based on data from studies on major open abdominal surgery showing superior pain relief and fewer respiratory complications compared with intravenous opioids.

Anesthetic Management

Although no trials exist, short-acting induction anesthesia agents such as propofol and dexmedetomidine and opioids such as sufentanil and remifentanil are widely used. Likewise, short-acting muscle relaxants are suggested. Deep neuromuscular block is usually necessary to ensure optimal access, particularly in laparoscopic surgery. Titration of anesthetic agents can be achieved using the bispectral index (BIS), thereby avoiding sedation that is too deep, which can be harmful in elderly patients [122]. Recent data suggest that a significant benefit on postoperative morbidity can be achieved by intraoperative low-tidal-volume ventilation [123].

Short-acting induction agents, opioids, and muscle relaxants are recommended. Maintenance should be guided by BIS. Low-tidal-volume ventilation is suggested.

Postoperative Nausea and Vomiting

A comparative non-randomized study [124] indicated that an enhanced recovery protocol with early mobilization, metoclopramide, and removal of the nasogastric tube on POD 1 or 2 reduced the rate of PONV after pancreaticoduodenectomy. Until further evidence becomes available for gastric cancer surgery, the suggestions for patients undergoing colorectal surgery [7] should be applicable. Patients with two risk factors—non-smokers, female, a history of motion sickness (or PONV), and postoperative administration of opioids [125, 126]—should be given prophylaxis with dexamethasone upon induction or a serotonin receptor antagonist at the end of surgery [127]. High-risk individuals (three risk factors) should receive general anesthesia with propofol and remifentanil and no volatile anesthetics, with dexamethasone 4–8 mg at the start of surgery, with the addition of a serotonin receptor

antagonist or droperidol [127] or 25–50 mg metoclopramide 30–60 minutes before the end of surgery [128]. A possible risk of impaired anastomotic healing caused by single-dose dexamethasone or other perioperative steroids is of concern but remains unclear [129–132].

Data from the literature on gastrointestinal surgery in patients at risk of PONV show the benefits of using different pharmacological agents depending on the patient's history of PONV, type of surgery, and type of anesthesia. Multimodal intervention, during and after surgery, is indicated.

Avoiding Hypothermia

Numerous meta-analyses and RCTs have shown that preventing hypothermia during major abdominal surgery reduces the occurrence of wound infections [133, 134], cardiac complications [134–136], bleeding and transfusion requirements [134–137], as well as the duration of postanesthetic recovery [138]. Prolonging systemic warming in the perioperative period (2 hours before and after surgery) confers further benefits [139]. There is even evidence to conclude that circulating-water garments offer superior temperature control to forced-air warming systems [140–142].

Intraoperative hypothermia should be avoided by using cutaneous warming in the form of forced-air or circulating-water garment systems.

Postoperative Glycemic Control

Morbidity and mortality after major gastrointestinal surgery are associated with insulin resistance [143] and plasma glucose levels [144]. Treatment of hyperglycemia with intravenous insulin in the intensive care setting improves outcomes, although hypoglycemia remains a risk. Core elements of enhanced recovery protocols alleviate postoperative insulin resistance and, therefore, also lower glucose concentrations [145, 146]. The most evident protocol items are avoidance of preoperative fasting and oral bowel preparation; use of oral carbohydrate treatment and stimulation of gut function by optimal fluid balance and avoidance of systemic opioids; and reduction of the stress response by use of EDA. Target thresholds for glucose are disputed, but glucosuria with the risk of hypovolemia will ensue when the renal threshold is exceeded at 12 mmol/l [147]. This level has been used as the control regimen in seminal studies and should [148, 149] probably be regarded as a limit, irrespective of settings.

Insulin resistance and hyperglycemia are associated with postoperative morbidity and mortality. Excessive hyperglycemia should be avoided as far as possible without introducing the risk of hypoglycemia.

Fluid Balance

Overload of salt and water and hypovolemia in the perioperative period all increase postoperative complication rates [150–153], suggesting that near-zero fluid balance should be achieved around the time of surgery. Deciding the correct amount required is complicated by the use of EDA as it causes vasodilatation and hypovolemia with hypotension—often diagnosed and treated as fluid depletion. This may result in the administration of unnecessary and large volumes of fluid [154]. To avoid unnecessary fluid overload, vasopressors should be considered for intraoperative and postoperative management of epidural-induced hypotension, bearing in mind the risk of drug-induced splanchnic vasoconstriction [155]. Several cardiac output monitoring devices provide dynamic indicators of fluid responsiveness and hemodynamic assessment. These vary from invasive pulmonary artery catheters to noninvasive pulse pressure analysis, bioimpedance, applied Fick principle, and Doppler imaging [156]. Intraoperative flow-guided fluid therapy with transesophageal Doppler ultrasonography to accurately assess and monitor fluid status has been shown to reduce complications and length of hospital stay after major abdominal surgery [157, 158]. All devices providing hemodynamic surveillance only show whether an increase in fluids infused actually leads to improved cardiac output, and not whether the patient actually has hypoperfusion in need of treatment. Data for high-risk patients (American Society of Anesthesiologists grade III) are lacking. Excessive use of 0.9% saline leads to an increase in postoperative complications compared with balanced crystalloids [159–161]. Although use of colloids results in improved blood volume expansion and less interstitial space overload than administration of crystalloids [162], there is no evidence from clinical trials or meta-analyses that they contribute to better clinical outcome [163].

Near-zero fluid balance as well as avoiding overload of sodium results in improved outcomes. High-risk patients need dedicated, individualized goal-directed fluid therapy handled by an experienced team to secure optimal tissue perfusion. A Doppler-guided technique may improve outcome. Balanced crystalloids should be preferred to 0.9% saline.

Comments

Although the magnitude of effect following the successful implementation of these guidelines is yet to be established, they represent an opportunity to apply the best available, updated perioperative practice to a group of patients at high risk of complications and morbidity.

For many of the items included, evidence is scarce and of low quality, and the use of a consensus-based process by an

international author group is an attempt to minimize these shortcomings.

Consensus was unproblematic for most of the procedure-specific items covered in these guidelines, with the exception of IN and access. Literature on the former subject is incongruent and further high-quality RCTs with single-component administration in enhanced recovery settings are needed to reach more definite conclusions and recommendations. The subject of access is complex. Although there is an abundance of literature confirming perioperative benefits of laparoscopic treatment and safety for distal gastrectomy, there is a significant learning curve and studies describing outcomes after total gastrectomy are still wanting. Furthermore, the oncological aspect of minimally invasive surgery for proximal gastric cancer remains largely undocumented in RCTs, as literature reporting long-term survival after total gastrectomy is limited and further studies are needed. Comparing laparoscopic and open resections in RCTs is challenging owing to the skill-dependent nature of these interventions and consequently a predictably low validity of the results [164]. Implementation of minimally invasive surgery for the treatment of gastric cancer, nevertheless, offers a potential evolution in the postoperative clinical course of these patients.

A recent review [165] on enhanced recovery in upper gastrointestinal surgery calls for international guidelines with standardization of clinical pathways, allowing comparison of results between institutions and across nations. The present consensus-based guidelines for enhanced recovery after gastrectomy offer such a framework, allowing the establishment of multi-institutional prospective cohort registries.

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Bariatric Surgery

43

Erik Stenberg and Anders Thorell

History and Background

Obesity is associated with several cardiometabolic comorbid diseases, increased risk for cancer, and a shorter expected lifespan. Over the last decades, obesity has evolved into a major public health threat all over the world. Bariatric surgery offers excellent long-term weight-loss results for most patients, as well as resolution or improvement of many of the comorbid diseases, reduced new onsets of cancer, and reduced overall mortality rates.

Ever since the first bariatric surgical procedure was performed by Dr. Henriksson in 1952 [1], the surgical technique has been improved, and new techniques have been developed. During the 1990s the minimal invasive technique was developed for bariatric surgery. With the evolvement of the technique, postoperative recovery has been improved and hospital stay, postoperative complications, and mortality rates have been reduced. The development of minimally invasive surgical techniques together with the increasing number of patients fulfilling the criteria for bariatric surgery has contributed to the enormous expansion in bariatric surgery seen during the last decades.

Today almost 500,000 bariatric operations are performed annually worldwide [2]. Although modern bariatric surgery can be considered to be safe with low perioperative complication and mortality rates, severe postoperative adverse outcome still occurs. Given the high number of operations performed annually, a large number of patients will still suffer from postoperative complications resulting in not only severe morbidity to the individual but also a large economic strain on the healthcare system.

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Although some factors related to patient characteristics may affect the risk of complications, several intraoperative and perioperative factors are of major importance for outcome after bariatric surgery [3, 4]. Introduction of perioperative evidence-based interventions may help in optimizing patients for surgery and improving safety and efficacy of the operation [5]. To date, only one randomized clinical trial comparing enhanced recovery after surgery (ERAS) with standard care for bariatric surgery has been performed—reporting a reduction of hospital costs and shortening of the length of stay by 1 day [6].

ERAS in Bariatric Surgery

Although there is no consensus concerning all details of the optimal perioperative care for the bariatric surgical patient, the ERAS pathway has been shown to offer a reduced stress response to the surgical trauma, and as a result thereof, reduced complication rates, improved pain and nausea control, as well as earlier mobilization and recovery (Fig. 43.1).

By adapting the surgical techniques and perioperative care to updated, evidence-based guidelines (Table 43.1), complication rates and mortality rates are low in bariatric surgery today. Although there are several parts of the perioperative care that have been well studied within the bariatric surgical field, many recommendations still have to rest on extrapolation of data from other surgical fields.

Preoperative Interventions

Even before the operation, several steps can be taken in order to optimize perioperative outcome. These steps include the selection of patients for surgery, preoperative information and weight loss, prehabilitation, cessation of alcohol use and smoking, as well as optimization of any comorbidities before surgery. Although several patient-related risk factors for postoperative adverse outcome are known today, the number

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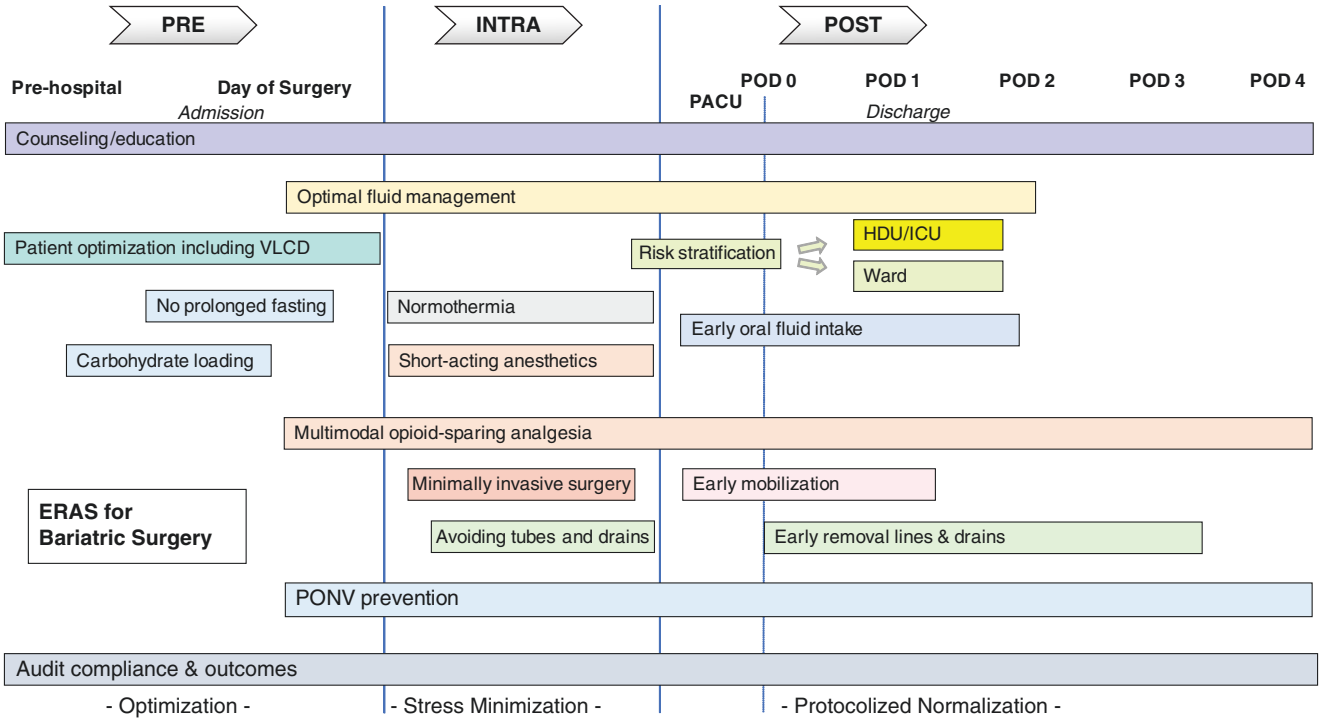

Fig. 43.1 General ERAS principles for bariatric surgery. VLCD very low-calorie diet, PACU postanesthesia care unit, HDU high-dependency unit, ICU intensive care unit, PONV postoperative nausea and vomiting

Table 43.1 Summary of recommendations for bariatric surgery

Element	Recommendation	Evidence	Recommendation
Preoperative care:			
Preoperative information	Preoperative information and education adapted to the needs of the patient should be provided. The education should include preparation before surgery, lifestyle modifications, types of surgery, expected perioperative course, surgical complications, realistic efficacy outcomes, and long-term management	Moderate	Strong
Prehabilitation and exercise	Due to limited data for bariatric surgery, no recommendations regarding prehabilitation can be given at present	Low	Weak
Smoking and alcohol	Cessation of smoking and alcohol at least 4 weeks prior to surgery reduces the risk for perioperative complications. A combination of education, repeated counseling, nicotine replacement therapy (for smoking) and abstinence prophylaxis (for alcohol dependency) seems to be the most effective approach. Due to an increased risk of alcohol abuse after bariatric surgery, patients with previous alcohol abuse should be abstinent for at least 2 years before surgery	High (smoking)	Strong (smoking)
		Moderate (alcohol)	Strong (alcohol)
Preoperative weight loss	A preoperative weight-loss regimen of 2–4 weeks on low-calorie diet with the goal of reaching a weight loss of 5–10% of the total body weight is associated with reduced risk for perioperative complications and better long-term weight-loss results and should therefore be adhered to	High (for postoperative complications)	Strong (for postoperative complications)
		Low (for postoperative weight loss)	Strong (for postoperative weight loss)
Preoperative fasting	Clear fluids can be allowed up to 2 hours before surgery and light meals up to 6 hours before surgery	High (nondiabetic obese patients)	Strong (nondiabetic obese patients)
		Moderate (diabetic patients without autonomic neuropathy)	Weak (diabetic obese patients with or without autonomic neuropathy)
		Low (diabetic patients with autonomic neuropathy)	

Table 43.1 (continued)

Element	Recommendation	Evidence	Recommendation
Carbohydrate loading	Due to lack of data for obese patients undergoing bariatric surgery, no firm recommendations can be given at present	Low	Strong
Premedication	Glucocorticoids can be used safely to prevent postoperative nausea and vomiting, but the effect is less clear with full adherence to all other aspects of the ERAS-protocol. No recommendations on preemptive analgesia can be given at present. Benzodiazepines should be avoided except in selected cases due to delayed recovery	Low	Strong
Intraoperative care:			
Anesthesia	Endotracheal intubation is the reference standard for bariatric surgery. Propofol for induction, avoidance of volatile anesthetics, minimization of opioids, and avoidance of fluid overload is recommended. Deep neuromuscular blockade should be used with monitoring of the degree of blockade using TOF. Pharmacological reversal of the blockade facilitates early recovery and is therefore recommended	Low	Strong
Fluid management	A conservative approach avoiding fluid overload should be preferred	Moderate	Strong
Surgical technique	Laparoscopy should be the standard approach for non-revisional bariatric surgery whenever possible. Complication rates are higher during the learning-curve period but can be reduced with active supervision for experienced bariatric surgeons. Nasogastric tubes should be used intraoperatively to facilitate leakage tests. In uncomplicated bariatric surgery, postoperative nasogastric tubes and abdominal drains should be avoided	High (laparoscopy) Low (nasogastric tubes) Low (abdominal drains)	Strong (laparoscopy) Strong (nasogastric tubes) Weak (abdominal drains)
Postoperative care:			
Thromboprophylaxis	A combination of compression stockings, early ambulation, and pharmacological prophylaxis using LMWH reduces the risk for VTE and is therefore recommended	High	Strong
Postoperative analgesia	Local wound infiltration either before skin incision or at the end of surgery reduces early postoperative pain and can be recommended. A multimodal approach using a combination of acetaminophen, NSAID/COX-2 inhibitors, and opioids (if necessary) should be used in the postoperative setting	High	Strong
Nutrition	Oral intake of clear fluids should be commenced already at the day of surgery with gradual introduction of liquid diet and eventually more dense protein sources	Moderate	Strong
Substitution of vitamins and micronutrients	Vitamin B12, multivitamins, and calcium + vitamin D should be routinely prescribed after bariatric surgery. Vitamin and minerals should be measured annually and deficiencies corrected when necessary	High	Strong

TOF train of four, *LMWH* low-molecular-weight heparin, *VTE* venous thromboembolism, *NSAID* nonsteroidal anti-inflammatory drug

of patients with so severe cardiovascular, pulmonary, or psychiatric comorbidity that surgery should be avoided will be small. For most patients, the increased risk associated with each factor is small in relation to other aspects of the perioperative care, and at present there are no models available to predict the risk of complications for the individual patient. Patient selection will therefore be discussed later in this chapter (see "Conclusions and Future Focus of Research" section).

Preoperative Information

Involving patients in the decision-making should be considered crucial in modern medicine, not least within surgical care. Although most patients fulfilling the criteria for bariatric surgery might consider that they do not have any realistic alternative, the decision to have major abdominal surgery with the obligation to make fundamental lifestyle changes and adhere to lifelong supplementation might be difficult to make for the individual patient [7].

Preoperative information and education of patients is therefore a necessary step in order to increase knowledge, ensure an accurate risk perception, reduce internal decisional conflicts, and increase the possibility to make active, well-informed choices. The information may also reduce anxiety, improve postoperative compliance, and result in shorter length of stay. Preferably, the information should focus on preparation before surgery and necessary lifestyle modifications, type of surgery, the expected perioperative course, potential complications, realistic efficacy outcomes, and long-term management. The information can be provided online and in individual or group sessions complemented by written information with more specific attention to specific

requirements during individual doctor-patient interaction. The ability to acquire and understand information differs between patients and may affect postoperative recovery. Preferably, the information and teaching methods should be adapted in order to ensure that all patients receive the necessary information in a way they can understand. Including peer support in this step may also be of benefit for the postoperative support.

Although a long time lapse between preoperative education and surgery may result in reduced knowledge, the optimal timing for this intervention remains unclear.

Prehabilitation and Exercise

Multimodal prehabilitation including exercise, nutritional assessment, and anxiety-coping interventions may improve functional capacity at the time of surgery and has been reported to reduce complication rates and length of stay after major abdominal and cardiothoracic surgery [8]. Despite being an attractive approach, there is still only limited data supporting the effectiveness of such prehabilitation programs. The applicability of the evidence is therefore yet to be decided for the obese patient undergoing bariatric surgery.

Smoking and Alcohol

Chronic smoking impairs lung function and the immune system, effects that may be reversed by smoking abstinence. Smoking increases the risk of severe postoperative morbidity after bariatric surgery, mainly related to infectious complications. Cessation of smoking from 4–8 weeks prior to surgery reduces postoperative complications after non-bariatric surgery, mainly wound and cardiovascular complications as well as need for secondary surgery [9, 10]. Although this risk reduction is not specifically evaluated in bariatric surgical patients, it appears reasonable to assume that similar effects can be achieved within this group of patients as well. Interventions beginning at least 4 weeks before surgery including weekly counseling and use of nicotine replacement therapy seem to be the approach to most likely impact complications and long-term smoking cessation [11].

High alcohol consumption (more than two standard drinks/day) is associated with an increased risk for postoperative adverse events—mainly infectious and cardiopulmonary complications, as well as complications related to wound healing. Although not studied specifically within the bariatric surgical field, the risks appear to be increased after most other types of surgery and seem to be particularly related to the consumption during the weeks most prior to the operation. Many of the negative effects of alcohol on organ functioning will improve already after a few weeks of alcohol abstinence. In fact, 1 month of abstinence in high consumers has been shown to markedly reduce the risk of postoperative complications [12]. A combination of education, abstinence prophylaxis, and disulfiram appears to have a very high success rate [13]. In addition to the increased risk of postoperative complications, the changes in alcohol absorption after both gastric bypass (Fig. 43.2) and sleeve gastrectomy (Fig. 43.3) might increase the risk for later alcohol overconsumption and alcohol dependency. It is, however, still not known if a period of preoperative alcohol cessation can reduce the risk for later alcohol overconsumption after bariatric surgery. Due to the increased risk of alcohol dependence, 1–2 years of abstinence before surgery is usually considered mandatory in patients with previous overconsumption [5].

Preoperative Weight Loss

A rapid reduction of weight during the last weeks before surgery has been shown to reduce liver volume and the amount of intra-abdominal fat. Accordingly, the surgeon's perceived complexity of the procedure also improves. A preoperative low-calorie diet (1000–1200 kcal/day) or a very low-calorie diet (800 kcal/day) with a goal of reaching a reduction of the total body weight by 5–10% is usually recommended [5]. The preoperative weight loss has been reported to be associated with a reduction of postoperative complications in the range of 12–56% [14, 15]. A preoperative weight loss might also be associated with improved long-term weight-loss results.

Based on current evidence, a preoperative weight-reduction regimen using 2–4 weeks of low-calorie diet is recommended. One concern is whether patients not achieving satisfactory weight loss, although being prescribed this diet, should be denied surgery or have this postponed. In addition, for patients with diabetes on glucose-lowering drugs (with risk of hypoglycemia), and patients with porphyria (with a risk of triggering relapse), evidence-based guidelines are lacking.

Preoperative Fasting

Anesthesia societies recommend intake of clear fluids and light meals up to 2 and 6 hours, respectively, before induction of anesthesia in healthy patients [16, 17]. Data from recent studies suggests that there is no difference in residual fluid volume, pH, or gastric emptying rates in obese compared to lean patients. Moreover, in healthy patients, there are no differences in residual gastric fluid volume and pH after drinking clear fluids up to 2 hours before surgery compared to after overnight fasting. The residual gastric fluid volume and pH also appear to be similar in obese diabetic patients (with or without autonomic neuropathy) as in non-diabetic patients. Intake of clear fluids up to 2 hours and light meals 6 hours before induction of anesthesia can therefore be recommended also in obese patients undergoing bariatric surgery [17].

Carbohydrate Loading

Preoperative carbohydrate loading, using iso-osmolar drinks containing complex carbohydrates ingested 2–3 hours before induction of anesthesia, reduces postoperative insulin resistance and nitrogen/protein losses and

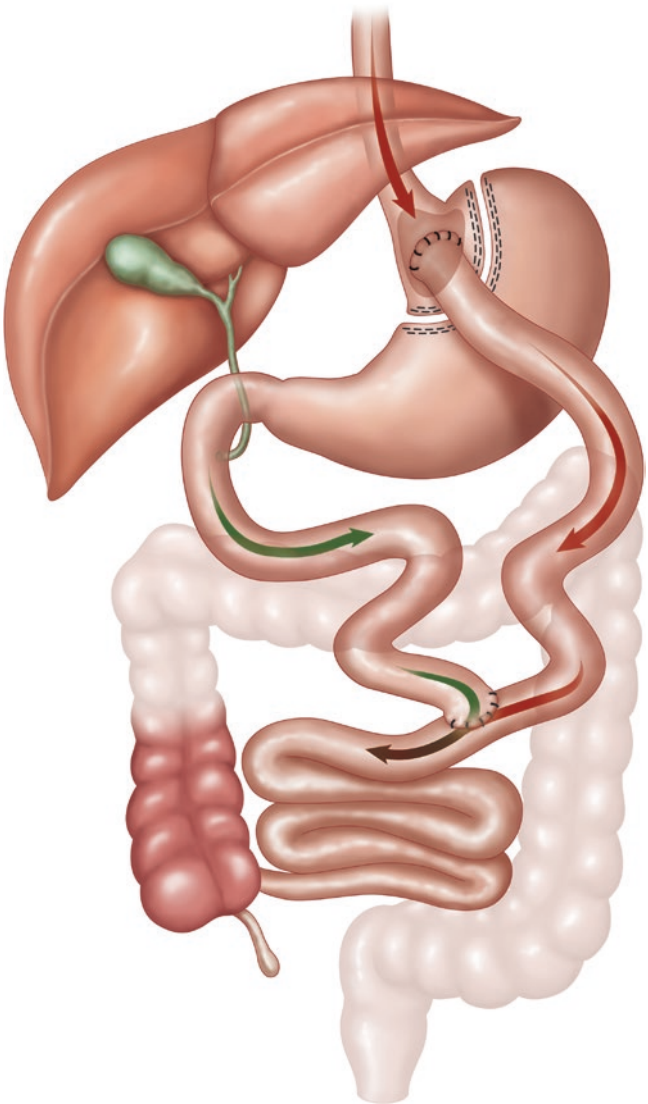

Fig. 43.2 Illustration of gastric bypass. (Published with permission from Ethicon – Johnson & Johnson)

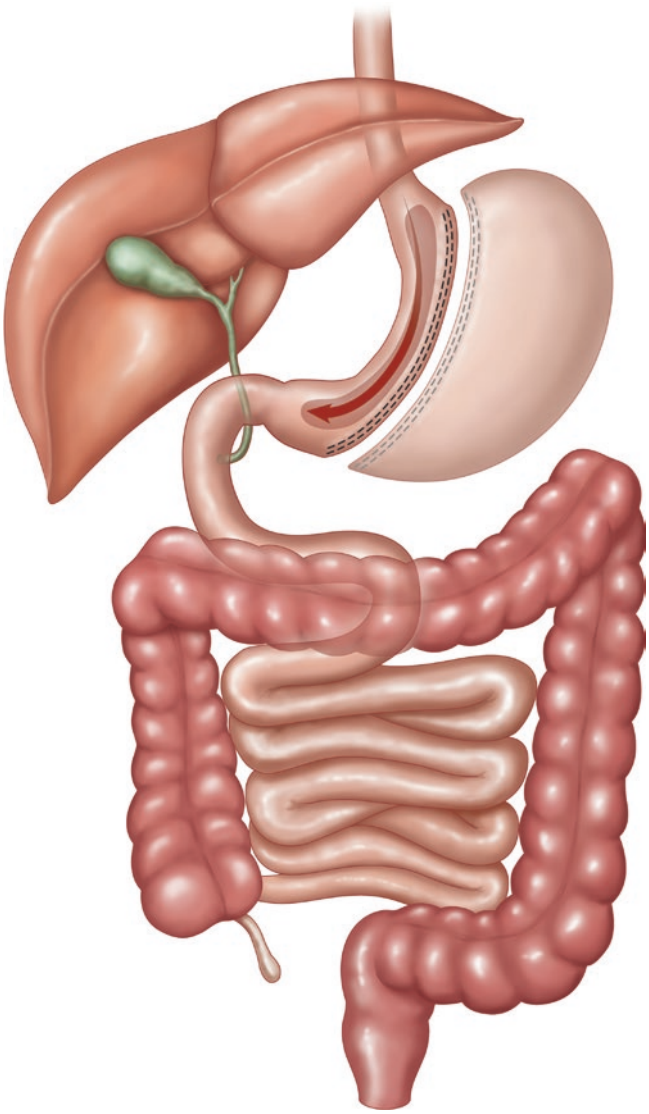

Fig. 43.3 Illustration of sleeve gastrectomy. (Published with permission from Ethicon – Johnson & Johnson)

maintains lean body mass after major abdominal surgery. In recent meta-analyses, a reduction of postoperative length of stay has also been demonstrated [18, 19]. This effect is most pronounced in patients undergoing major surgery. Preoperative carbohydrate loading can be used safely in bariatric surgery, also in patients with type 2 diabetes. When given to nonobese patients with type 2 diabetes, no differences in gastric emptying rates were noted compared to healthy subjects. It does not seem to increase the risk of hyperglycemia or aspiration, but in a comparative study, patients with type 2 diabetes reached higher postprandial glucose peak and slower reduction to normal levels [20]. Compliance to preoperative carbohydrate loading has been reported to be as low as 15% in bariatric surgery, and no difference in overall postoperative complication rates has been reported [6, 21]. There are conflicting data reported as to the effect of carbohydrate loading on postoperative nausea and discomfort. Therefore, no evidence-based recommendations regarding the use of preoperative carbohydrate loading can be given for bariatric surgery at present.

Premedication

Premedication may be administered mainly in order to reduce preoperative anxiety and postoperative pain and nausea.

Due to their anti-inflammatory and antiemetic effect, glucocorticoids have been used to reduce the stress-response to elective surgery and to prevent postoperative nausea and vomiting (PONV). In a meta-analysis of 11 randomized clinical trials, no effect on complication rates and length of stay was seen [22]. For bariatric surgery, results from a retrospective analysis of 2000 consecutive patients suggested that a

steroid bolus was a predictor for successful outpatient discharge [23]. However, no effect on postoperative nausea was seen in a randomized trial of 100 patients comparing glucocorticoids with no glucocorticoids in gastric bypass surgery within an ERAS-protocol [24]. The safety of a single dose of glucocorticoids has been addressed in two meta-analyses, showing no increase in the risk for adverse outcome [22, 25]. However, if glucocorticoids are given, blood glucose should be monitored intra- and postoperatively to avoid hyperglycemia, which is associated with increased postoperative, mainly infectious, complications.

Pain during and after surgery may induce sensitization, with a risk of subsequent transformation into chronic pain. However, the main purpose of pain treatment is to alleviate discomfort and reduce anxiety. A preemptive analgesia is thought to decrease postoperative hyperalgesia and thereby the magnitude and duration of postoperative pain. Although preemptive analgesia provides a theoretical benefit, clinical trials in humans have reported inconsistent results with questionable generalizability to minimally invasive bariatric surgery. Non-opioid analgesia (in particular with COX-2 inhibitors and gabapentin) has more recently been shown to reduce postoperative pain if given in the preoperative setting. For bariatric surgery, results from a randomized clinical trial including 60 patients indicate that 300 mg of gabapentin given in the preoperative setting may reduce postoperative pain and nauseas/vomiting as well as need for opioids [26].

Anxiety is common in the preoperative setting. Pharmacological treatment, traditionally by the use of benzodiazepines, offers a potential relief. In a randomized trial of 1062 patients, however, benzodiazepines did not improve patients' experience but were associated with longer time until endotracheal extubation and delayed cognitive recovery [27]. Melatonin may be an alternative option to benzodiazepines. In a meta-analysis of 12 randomized controlled trials (RCTs), melatonin given preoperatively reduced preoperative anxiety compared to placebo. The effect was less clear in the postoperative setting [28]. In a small, randomized trial comparing melatonin to placebo in bariatric surgery, a reduction of postoperative pain, and improvement in quality of postoperative recovery was reported [29].

Intraoperative Interventions

Anesthesia

The bariatric surgical patient usually has several risk factors for postoperative nausea and vomiting (PONV), a high risk for difficult airway access, and may also be difficult to bag and mask ventilate. Endotracheal intubation remains the reference standard for airway maintenance in bariatric surgery. The tubes should be correctly sized in order to reduce the risk for micro-aspiration and pulmonary complications [5]. A "ramped" position, aligning the auditory meatus and the sternal notch horizontally, has been reported to be a superior technique to obtain a good laryngeal view during direct laryngoscopy.

Various volatile agents have been compared in bariatric surgery, with a small advantage in terms of earlier extubation and recovery of mental functioning for short-acting agents with lower absorption [5]. In a randomized clinical trial of 119 patients, an opioid-free, intravenous anesthetic technique using propofol for induction and maintenance of anesthesia was associated with marked reduction of PONV compared with balanced anesthesia [30]. Although other prospective comparisons of the anesthesiological techniques in bariatric surgery are lacking, the use of propofol, avoidance of volatile anesthetics, minimization of opioid use, and avoidance of fluid overload (see below) can be recommended.

Although not studied specifically in the bariatric setting, a low-tidal volume ventilation has been shown to improve clinical outcomes in patients with intermediate to high risk of pulmonary complications after major abdominal surgery. A combination of positive end-expiratory pressure and recruitment maneuvers may improve oxygenation and pulmonary mechanisms.

Good visualization facilitates the laparoscopic surgical procedure. High pressure pneumoperitoneum may, however, affect the microcirculation of the bowel and the renal cortex as well as cardiac output. A deep neuromuscular blockade allows adequate surgical access and visualization while avoiding over pressure pneumoperitoneum. Residual neuromuscular blockade is, however, common in the early postoperative period and associated with an increased risk of pulmonary complications. Train of four (TOF) provides objective data on the degree of neuromuscular blockade and should preferably be monitored routinely in laparoscopic bariatric surgery. A TOF > 0.9 is associated with earlier recovery, improved patient satisfaction, and a reduced risk for residual blockade and thus also a reduced risk for pulmonary complications. Reversal of neuromuscular blockade using acetylcholine esterase inhibitors or selective cyclodextrin binding (sugammadex) is a safe and effective measure to reduce the incidence of residual blockade and to facilitate earlier recovery.

Fluid Management

Morbidly obese patients optimized in the preoperative setting with rapid weight loss might be hypovolemic at the time of surgery, which has been reported in up to 71% of patients [31]. In combination with other risk factors—such as male sex, higher body mass index (BMI) (>52 kg/m^2), and in particular, prolonged operation time—rhabdomyolysis may occur with a high risk for acute renal failure. However, in a single-center, retrospective analysis, the incidence of acute

renal failure was 2.3% with full resolution among all patients who had a normal renal function preoperatively [32].

Although obese patients have an increased total blood volume, the volume/body weight is less than that in nonobese (in the range of 50 mg/kg compared to 75 mg/kg). After elective, open abdominal surgery, the risk of transient hypervolemia in response to liberal volume infusion is relatively high, with a potential risk for postoperative complications and prolonged length of stay. In bariatric surgery, aggressive fluid therapy (>2000 mL/h) has been suggested to reduce the risk for rhabdomyolysis, postoperative nausea and vomiting, renal failure, and length of stay. With a more conservative approach (15 mL/kg/h) compared to liberal intraoperative fluid volume (40 mL/kg/h), no difference in the incidence of rhabdomyolysis was seen [33]. In a randomized clinical trial comparing low volume (4 mL/kg/h) with high volume (10 mL/kg/h) infusion, no difference in urine output was seen [34].

During standard laparoscopic bariatric surgery, a conservative, low-volume approach can therefore be recommended.

Surgical Technique

The use of laparoscopic technique in bariatric surgery reduces hospital stay and postoperative complications, is associated with a more rapid recovery and improvements in quality of life as well as a marked reduction in abdominal wall hernias compared to open surgery. Due to lack of adhesions, the laparoscopic approach is, however, associated with an increased risk of small bowel obstruction caused by internal hernia. Routine intraoperative closure of the mesenteric defects will markedly reduce this risk [35]. The higher immediate costs related to laparoscopic surgery has been estimated to be well compensated for by the reduction in complication rates, the shorter hospital stay, and the more rapid recovery [36].

During the learning curve period, operation times and complication rates are higher. This period can be expected to be in the range of 50–100 operations for the individual surgeon and up to 400 operations when gastric bypass is introduced at a center. The learning curve can be shortened if there is substantial previous experience from advanced laparoscopic surgery and by active supervision from experienced bariatric surgeons. Furthermore, the number of bariatric surgical procedures performed annually at the center is associated with reduced risk of postoperative complications, at least up until a volume in the range of 200 operations/year.

Abdominal Drains and Nasogastric Tube

Abdominal drains may be placed with the intention to detect postoperative gastrointestinal leaks or bleedings. The sensitivity of detecting such leaks has been reported to vary between 0% and 94%. The risk of failure for conservative, non-operative management of leaks is also high. At present there are no RCTs published evaluating routine abdominal drainage in bariatric surgery. In modern laparoscopic bariatric surgery, leak rates can be expected to be as low as 0.8–1.6%, and the use of prophylactic drains does not appear to reduce leaks and reoperation rates. Despite lack of evidence in bariatric surgery, routine abdominal drainage is, thus, likely to be unnecessary.

Although postoperative anastomotic leaks are relatively uncommon, they may have severe consequences. Leaks can occur from locations such as the suture line of the gastroenterostomy and the back wall of the gastric pouch in gastric bypass surgery (Fig. 43.2). Many of these leaks can be detected through an intraoperative leak test using air or methylene blue, or through intraoperative gastroscopy with a combination of air insufflation and visual inspection. A leak test does not appear to reduce the risk for leaks after sleeve gastrectomy (Fig. 43.3).

In a Cochrane meta-analyses, it was recommended that postoperative nasogastric tubes should only be used selectively in open abdominal surgery [37]. In the same report, a subgroup analysis of gastroduodenal surgery showed an increased risk of pulmonary complications associated with routine postoperative nasogastric tubes. Also, routine use of nasogastric tubes may prolong the time until resumption of oral diet after gastric resection for cancer. In a retrospective, single-center analysis, no difference in complication rates was seen without postoperative nasogastric tubes compared to routine usage after gastric bypass surgery [38]. Based on current knowledge, the routine use of intra-abdominal drains or nasogastric tubes cannot be recommended in uncomplicated bariatric surgery.

Postoperative Interventions

In order to reduce the risk for serious complications, focus in the immediate postoperative phase should be on adequate analgesia and early mobilization. Immediate postoperative tissue oxygenation has been reported to be lower in obese patients compared to nonobese [39]. Supplementary oxygen may therefore be needed within the first 24 hours postoperatively. Furthermore, a head-elevated, semi-sitting, or prone position should be adapted in order to prevent pulmonary atelectasis.

Thromboprophylaxis

Morbid obesity is in itself a risk factor for venous thromboembolism (VTE), which also remains one of the more common causes for mortality after bariatric surgery. In addition, morbidly obese patients often have other risk factors such as mobility limitations and a sedentary lifestyle. Other known risk factors are previous history of VTE, venous insufficiency, chronic heart failure, male gender, and older

age. Chemoprophylaxis reduces the risk for postoperative VTE after non-orthopedic and bariatric surgery, although adherence after discharge can be expected to be low. Low-molecular-weight heparin (LMWH) has the advantage of a more predictable dose response, increased bioavailability, and longer plasma half-life compared to unfractionated heparin, allowing once-daily dosing. LMWH has also been reported to be equal or better than unfractionated heparin in terms of safety and efficacy and should be considered routine in modern bariatric surgery. Patients with high risk may benefit from a prolonged prophylaxis of 3–4 weeks, although the effect is questionable in an otherwise optimized perioperative care using a fast-track program. Mechanical prophylaxis with sequential compression stockings and early ambulation may further reduce the risk of VTE after surgery. With application of these preventive measures, the rate of VTE can be expected to be as low as 0.1–0.25% after laparoscopic bariatric surgery.

Although theoretically promising for patients at high risk for venous thromboembolic complications, vena cava filters cannot be recommended at present due to the risk for adverse events and lack of evidence for its efficacy.

A combination of LMWH, sequential compression stockings, and early ambulation should be considered a standard part of modern bariatric surgery.

Postoperative Analgesia

An effective postoperative control of pain facilitates early mobilization with improved pulmonary functioning and overall experience of the operation. Acute pain in the perioperative setting develops secondary to the tissue trauma and direct nerve injury causing a combination of central and peripheral pain. The use of sedative drugs and opioids can be effective in reducing pain but may expose the bariatric surgical patients to drug-related side effects, upper airway obstruction, and postoperative hypoxemia. A multimodal approach using a combination of medication and local or regional anesthetics is likely to give the best pain control [40]. At the same time, patients at risk for postoperative pain should be recognized. Women, patients with preexisting pain, and younger ages have been reported to have increased risk for postoperative pain after various types of surgery. After laparoscopic bariatric surgery, younger age and preexisting pain have been reported to be the strongest risk factors for severe postoperative pain.

A combination of opioids, nonsteroidal anti-inflammatory drugs (NSAIDs)/COX-2 inhibitors, and acetaminophen/paracetamol reduces pain intensity and opioid consumption compared to standard non-multimodal, opioid-based treatment. NSAID/COX-2 inhibitors should be used cautiously in risk groups due to a small increased risk for bleeding and renal failure after major abdominal surgery. Although a small decrease in hemoglobin has been reported in small observational studies, the risk of severe complications related to ulcers and anastomotic leaks from limited doses of NSAIDs has not been reported in bariatric surgery. Furthermore, the use of ketorolac as part of a multimodal analgesia in bariatric surgery may effectively reduce pain during the first postoperative day [41, 42].

Wound infiltration of local anesthetics can be administered safely and has been reported to reduce postoperative pain during the first 4–8 hours after surgery. Although the quality of evidence remains weak, there seems to be no difference whether local anesthetics are administered before skin incision or at the end of surgery. After the first postoperative hours, there appears to be no improvement in pain experience or return to normal activities with the use of local anesthetics.

Thoracic epidural analgesia improves pulmonary function after open abdominal surgery, but does not seem to have the same benefits as patient-controlled analgesia or intravenous morphine after laparoscopic surgery, and can therefore not be recommended for routine use in laparoscopic bariatric surgery [5].

Nutrition and Substitution of Micronutrients

Patients undergoing bariatric surgery should resume oral intake of clear liquids already at the day of surgery. Although the evidence level remains low, a liquid diet should be adhered to during the first 2 postoperative weeks, after which soft, moist, or diced protein sources should be introduced. After 4 weeks, a standard diet is usually well tolerated.

Deficiencies of vitamins and minerals are common among morbidly obese patients before surgery, and even more so after bariatric surgery. Vitamin B12 absorption is dependent on intrinsic factor and if not substituted, deficiency might likely appear after gastric bypass, sleeve gastrectomy, and duodenal switch operations. Iron deficiency is also not uncommon, in particular among menstruating women and adolescents. Without substitution of calcium and vitamin D, patients are at risk for secondary hyperparathyroidism resulting in bone resorption and ultimately higher risk for fractures. All bariatric surgical patients should therefore receive supplementation with vitamin B12 (1 mg daily), multivitamins (twice daily containing a minimum of 1.4 mg thiamin, 400 µ[mu]g folate and 14 mg zinc), and calcium + vitamin D (500 mg/800 IE twice daily)—although the optimal dose of vitamin D and calcium is still a matter of debate. Iron deposits should be monitored and supplemented when necessary. Adherence to recommended supplementation has been reported to be as low as 52–83% at 5 years after surgery [43].

Groups of Patients Requiring Specific Considerations

Diabetes

Depending on the definition, the incidence of diabetes in patients undergoing bariatric surgery has been reported in

the range of 15–34%. Gastric bypass, duodenal switch, and sleeve gastrectomy are all effective treatments for diabetes. The improvement in glucose homeostasis occurs early after the operation due to a combination of caloric restriction, changes in secretion of gut-derived hormones and nutrient flow [44]. For patients with type 2 diabetes, there is low-grade evidence supporting discontinuance of insulin secretagogues, while insulin doses should be adjusted postoperatively to minimize the risk of hypoglycemia. Treatment with metformin should be continued until prolonged resolution of diabetes is verified. Glucose should be monitored closely and insulin therapy used when necessary, aiming at a fasting blood-glucose <6.1 mmol/l (<110 mg/dl) and postprandial blood-glucose <10 mmol/l (<180 mg/dl) [45].

Sleep Apnea

In a bariatric surgical population, as many as 40–44% may suffer from moderate to severe sleep apnea, of which many are previously undiagnosed. Untreated sleep apnea and hypoxemia in the perioperative phase are factors associated with increased risk for postoperative complications. The STOP-Bang questionnaire for preoperative screening for sleep apnea has a high predictive value and is recommended in the preoperative evaluation of candidates for bariatric surgery [46]. Oxygen therapy alone may increase the risk of apnea/hypopnea postoperatively. A combination of oxygen and positive airway pressure support is preferred for patients with sleep apnea. Patients using continuous positive airway pressure (CPAP) at home should continue their treatment in the postoperative phase. Compliance with CPAP treatment may, however, be as poor as 50–80% [47]. Patients with symptoms of sleep apnea but not given positive pressure treatment should be monitored closely. An oxygen saturation <90% during the postoperative period may indicate a need for positive airway pressure treatment. For patients with sleep apnea, intraoperative anesthetic and surgical factors play the most important role for the need of positive pressure ventilator support. Short-acting anesthetic drugs and restrictive use of opioids should be considered for this group of patients [5].

Conclusion and Future Focus of Research

With increasing volumes and adherence to evidence-based perioperative interventions, bariatric surgery today is safe with satisfactory results in terms of sustained weight loss and improvement/resolution of obesity-associated comorbidities in most patients. However, as in all areas of surgical care, some patients undergoing bariatric surgery still experience less satisfactory outcome than expected, such as those suffering from postoperative complications or unsatisfactory weight development. Moreover, in a small but significant number of patients, long-term adverse events including chronic abdominal pain, postprandial hypoglycemia, or nutritional deficiencies are seen.

Therefore, in order to further improve outcome after bariatric surgery, some specific aspects of perioperative care might deserve particular attention, such as selection of patients, adherence to follow-up, and use of optimal surgical technique.

Several patient-related risk factors are known to be associated with increased risk of postoperative adverse outcome, such as high age, cardiovascular and pulmonary diseases, diabetes, depression, gastroesophageal reflux, mobility limitations, previous venous thromboembolism, bleeding disorder, and BMI in the extremes [3, 48–50]. These risk factors should be identified during the preoperative assessment and, if possible, optimized before surgery, which has been shown to reduce complication rates. However, for preoperative identification of patients at risk for chronic abdominal pain, poor weight development, or loss to follow-up with nutritional deficiencies, sufficient knowledge is still lacking and therefore constitutes an important area for future research. With such increased knowledge, improved selection of the patient to optimal obesity treatment, being surgical or non-surgical, should be possible.

Another important area with room for improvement is objective data regarding which surgical technique that is optimal to use. Worldwide, Roux-en Y gastric bypass (RYGB) and sleeve gastrectomy (SG) are the two most commonly used techniques (Fig. 43.2 and Fig. 43.3), together constituting more than 90% of all procedures. Although available data suggest that there are no major differences between these two in terms of efficacy or adverse events at short- or median-time follow-up, the possible superiority of any of these in the long-term is yet to be decided. In order to address this and other similar research questions, large-scale multicenter RCTs need to be conducted with sufficient long-term follow-up. In Sweden, such a study is presently running, in which 17 participating centers are including patients that are being randomized to SG or RYGB, respectively with 5 years follow-up (Clin Trials.gov Identifier NCT02060630). An important aspect is that the number of included patients in such a study should be sufficiently high in order to enable analysis within relevant subgroups such as by sex, BMI, age, or presence of diabetes. If there is access to a national or regional registry that could be used as a base for registration of study data, this might be associated with several major advantages as has been shown previously regarding closure of mesenteric defects in RYGB by use of the Scandinavian Obesity Surgery Register (SOReg) [35]. Other examples of areas in which there is a need for proper evaluation before being introduced in routine bariatric clinical practice are new techniques such as “single-anastomosis gastric bypass” or the use of robotic surgery.

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ERAS for Major Urological Procedures: Evidence Synthesis and Recommendations

44

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ERAS in Urology: Background

Rationale for Enhanced Recovery Pathways in Urology

Despite substantial improvement of anesthetic and surgical technique in different fields over the past years, postoperative complications remain one of the major drawbacks of surgery for the patient but also for the surgeon and the care team. Assuming no anesthetic or surgical failure occurs, one of the main pathogenic factors leading to postoperative morbidity is the so-called surgical stress response [1].

Enhanced recovery after surgery (ERAS) is a multimodal concept combining preoperative, perioperative, and postoperative evidence-based elements aiming to reduce surgical stress. First developed and applied to colorectal surgery in the 1990s [2], ERAS principles have been shown to significantly reduce morbidity, length of stay (LOS), and total costs [3–5].

Radical cystectomy (RC), including bilateral extended pelvic lymphadenectomy, is considered to be one of the most significant complication-prone surgeries in urology, and still remains a very invasive surgical procedure. Morbidity after both open and robotic-assisted RC (RARC) with urinary diversion or neobladder reconstruction has been estimated to be up to 60% [6, 7]. Therefore, RC patients may be ideal candidates for an ERAS pathway (Fig. 44.1) in order to potentially benefit from less surgical stress and postoperative complications.

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ERAS guidelines, issued from colorectal surgery, might not be applied identically to bladder cancer patients as the surgical procedure itself differs widely (small bowel anastomosis, risk of renal insufficiency in obstructive bladder tumors, urine within the peritoneal cavity during and after surgery, both extra- and intraperitoneal access, longer operative time, increased risk of blood loss). Moreover, colorectal ERAS items, such as the avoidance of urinary and abdominal drains, might not be fully applicable to RC patients [8]. It is therefore of utmost importance to tailor each ERAS protocol elements to the specific surgical procedure of interest. In urology, initial efforts have therefore been undertaken to develop ERAS protocols specific for open RC because of its surgical challenge, rather than for radical prostatectomy (RP) or nephrectomy, which are more frequent but less invasive [8, 9].

Background and History of the ERAS® Society – Urology Chapter

Based on Kehlet's work and hypothesis that reducing surgical stress through multimodal, evidence-based perioperative care could improve a patient's recovery, a group of pioneers created the ERAS study group in 2001. They soon discovered that there was not only a great discrepancy between the actual practice and what was already known in the literature to be the best practice, but surprisingly they noticed also a wide variation between institutions [10].

The ERAS study group evolved over the years, and the ERAS® Society was created in 2010. In 2012, the first International ERAS® World Society congress was held in Cannes, France, with 237 delegates from 28 countries, including key players from different subspecialties. During this congress, a small group of urologists and anesthesiologists decided to adopt ERAS principles and adapt them to RC. A systematic literature review was undertaken, and this fruitful collaboration resulted in the publication of the first ERAS recommendation for RC in 2013 [9]. The ERAS®

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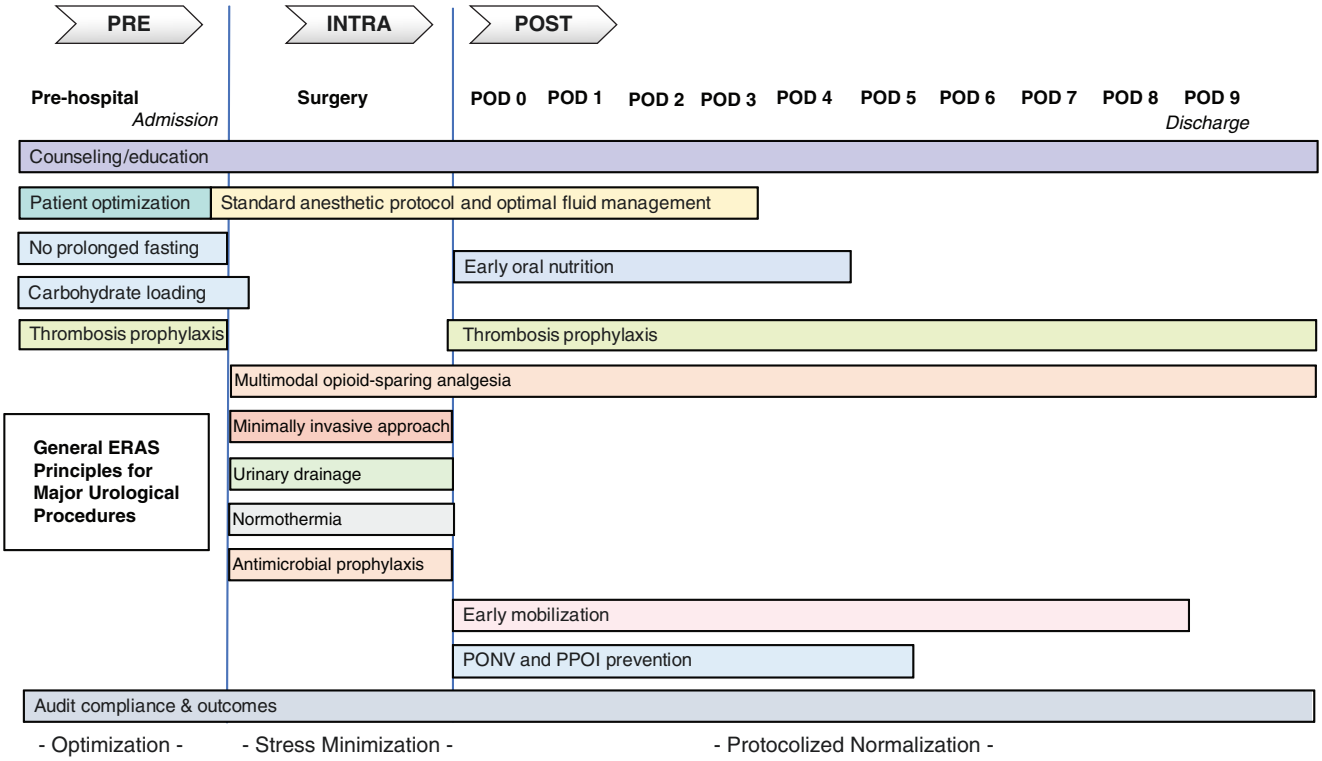

Fig. 44.1 General ERAS principles for urology. PONV postoperative nausea and vomiting, PPOI prolonged postoperative ileus

Society – Urology Chapter was then officially recognized in 2014. Since then, many original studies adopting these guidelines have been published [11]. The ERAS Urology guidelines have been then adapted to RARC [12]. The ERAS Urology group has now matured to a core group of about 10–12 people involved in the improvement of RC guidelines and the development of new guidelines for radical nephrectomy and RP, with the goal of increasing the awareness of the ERAS program in urology worldwide. It is important to note that this collaborative and structured effort was neither the first nor the only one toward the development of enhanced recovery principles applicable to urology. However, to our knowledge, the ERAS urology guideline was the first one to incorporate a fully documented protocol including more than 20 evidence-based elements (Table 44.1).

Summary of ERAS Guideline for Urological Surgery

A non-systematic review of the literature through the electronic databases MEDLINE, EMBASE, and Web of Science was performed, using the keywords "ERAS," "radical cystectomy," "radical prostatectomy," "radical nephrectomy," "enhanced recovery," "surgery," "colorectal," "prognosis," and "survival." In particular, the retrieved articles for data on ERAS for urological surgery were screened, with emphasis on studies published between 2012 and 2017. The evidence included in this chapter was based on the consensus of all authors.

The Preoperative Phase

Preoperative Counseling

Adequate preoperative counseling, using verbal or written materials, diminishes anxiety, postoperative complications, and reduces the average LOS [13, 14]. Indeed, an active participation of the patient to his or her own postoperative recovery seems to have a positive impact on the healing process because of a better adherence to ERAS criteria [14–17]. Social status assessment, stoma management, or neobladder care appear to be critical points for early discharge.

Preoperative Optimization

Comorbidities such as hypertension, diabetes, and anemia should be anticipated and corrected before surgery. This is especially true in the era of neoadjuvant chemotherapy. Avoidance of tobacco exposure and reduced alcohol consumption have shown beneficial effects on surgical outcomes and complications [15, 16]. Improvement of the preoperative nutritional status is also a crucial point. It has been estimated that around one-fifth of urological patients are malnourished and could benefit from preoperative nutritional supplements,

Table 44.1 Overview of care plan and proposed interventions for each ERAS item

ERAS items	Surgeon	Anesthesiologist	Nurse/dietician/stoma specialist
1. Counseling and education	Counseling, stoma education and identification of best location		
2. Medical optimization	Risk factors correction Prehabilitation		Intervention on request if malnourished
3. Oral mechanical bowel preparation	Should be avoided		
4. Preoperative fasting		Solids: 6 hours optimal Clear fluids: 2 hours optimal	
5. Carbohydrates loading			2 hours preoperatively
6. Preanesthesia medication		Avoid long-lasting drugs	
7. Thromboprophylaxis	LMWH 12 hours prior to surgery, 6 hours postoperatively Should be prolonged 1 month from discharge		Compressive stocking or intermittent pneumatic compression
8. Analgesia	CWI	TEA	
9. Minimally invasive approach	Clear evidence for nephrectomy Use of surgeon's best mastered approach for RP and RC		
10. Resection site drainage	No routine use		
11. Antimicrobial prophylaxis and skin preparation	Single perioperative course of a 2nd- or third-generation cephalosporin		
12. Standard anesthetic protocol	Refer to consensus statement		
13. Perioperative fluid management		Restriction vs liberal remains to be assessed	
14. Preventing intraoperative hypothermia		Forced air warming	
15. Nasogastric intubation	No routine use		
16. Urinary drainage	Ureteroileal stenting		
17. Prevention of postoperative ileus	Multimodal approach Alvimopan Minimally invasive Ureteroileal stenting	Optimized fluid management	Early oral diet Early mobilization
18. Prevention of PONV	Multimodal approach	Optimized fluid management	
19. Postoperative analgesia	Paracetamol/NSAID CWI	TAP block TEA	
20. Early mobilization	Recommended		
21. Early oral diet	Recommended		
22. Audit	Recommended		

LMWH low-molecular-weight heparin, *CWI* continuous wound infiltration, *TEA* thoracic epidural analgesia, *RP* radical prostatectomy, *RC* radical cystectomy, *PONV* postoperative nausea and vomiting, *NSAID* nonsteroidal anti-inflammatory drug, *TAP* transversus abdominis plane

reducing the risk of anastomotic leaks and infections [17]. In RC patients, malnutrition appears to be a strong predictor factor of mortality at 3 months (HR 2.91; $p < 0.01$) [18]. In colorectal surgery, preoperative immunonutrition seems to reduce the LOS and the rate of infectious complications compared to conventional nutritional supplements [19], but few data are available for RC [20–22]. Preoperative enteral immunonutrition for RC patients could have a benefit in reducing major complications, such as infections and ileus [23]. Recent evidence indicates that preoperative physical exercise, nutritional support, and stoma education improves health-related quality of life [24]. These interventions should be considered as an extension of ERAS protocol in all patients undergoing major urological surgeries and a possible way to alleviate the recovery burden.

Oral Mechanical Bowel Preparation

There is a high level of evidence suggesting to avoid any bowel preparation prior to RC [25, 26]. However, prior to RARC with intracorporeal urinary reconstruction, it is recommended to avoid only vegetables and any fiber-rich nutritional elements 24 hours before surgery, in order to reduce spillage from the intra-abdominally opened ileum [12].

Preoperative Fasting

Preoperatively, solid foods and clear fluids (including preoperative carbohydrate loading [PCL]) must be prohibited for 6 hours and 2 hours, respectively, in order to ensure safe intubation. However, prolonged fasting and fluid abstention is detrimental to optimal preparation against surgical stress [27].

Preoperative Carbohydrates Loading

Metabolic preparation for surgery using preoperative carbohydrate loading (PCL) 2–4 hours prior to anesthesia seems to reduce anxiety and postoperative insulin resistance, and at the same time, it maintains body weight, with a positive impact on LOS. For colorectal surgery, PCL has been found to be an independent predictor of improved postoperative clinical outcomes [15, 28, 29]. However, no data on urologic procedures are available to date. Concerns remain in diabetic patients.

Preanesthesia Medication

Pharmacological management of anxiety prior to surgery should be limited to a well-selected group of patients and administered using short-acting sedation. Long-acting drugs may lead to delayed mobilization and oral intake and overall a reduced adherence to the recovery protocol. Careful use in the elderly population is recommended given the risk of induced cognitive impairment and paradoxical delirium [15, 30].

Thrombosis Prophylaxis

Patients undergoing RC are at high risk of postoperative deep vein thrombosis (DVT) with an incidence of 5% within 30 days of surgery, despite adequate prophylaxis. Age, race, gender, smoking status, medical comorbidities, extended lymph node dissection, and procedure length are identified as independent risk factors [31, 32]. Patients treated with cisplatin-based neoadjuvant chemotherapy have an additional risk of DVT and should be carefully followed [33].

An injection of low-molecular-weight heparin (LMWH) is recommended 12 hours prior to surgery and can be repeated as early as 6 hours after surgery, without any increased risk of bleeding complications [34]. Since VTE has been linked with increased 30-day and 2-year mortality, prolonged prophylaxis in high-risk patients is recommended [35–37]. The use of compression stocking is a valuable strategy to reinforce pharmacological prophylaxis, particularly if there is delayed mobilization [38]. Intermittent pneumatic compression could be considered for high-risk cancer surgery as a mechanical prophylaxis [39].

The Surgical Phase

Analgesia

There is strong evidence in open colorectal surgery of the benefit of 48- to 72-hour thoracic epidural analgesia (TEA), as better pain control appears to facilitate overall recovery with lower complications rate and opioid consumption [15, 40]. In RC, TEA showed better outcomes and its superiority compared to patients treated with intravenous (IV) morphine analgesia [41, 42]. Rectus sheath catheters could be a safe and efficient alternative to TEA in urologic surgery [43, 44]. A randomized clinical trial is ongoing comparing 36-hour bupivacaine/fentanyl TEA to rectus sheath catheters in major abdominal surgery including RC [45].

Minimally Invasive Approach

RARC with extra- or intracorporeal urinary diversion is raising interest alongside early recovery protocols. On a surgical point of view, RARC appears equivalent to the open approach in terms of major complications. However, intraoperative blood loss, abdominal wall complications rate and LOS are reduced according to several clinical trials [7, 12, 46]. These results remain to be assessed in appropriately powered studies with equivalently experienced surgeons. On the oncological point of view, RARC seems to have similar disease recurrence rate, cancer-specific survival, and overall survival compared to open RC [47]. Interestingly, a recurrence pattern analysis found a potential increased risk of local abdominal recurrence rate in RARC patients. According to the results of the LAFA study, the highest LOS reduction was found combining a minimally invasive approach with the ERAS protocol [48]. Similar evidence has been found in robotic-assisted pancreatoduodenectomy [49].

Resection Site Drainage

A meta-analysis in colorectal surgery demonstrated no difference in anastomotic leaks and overall outcomes with or without peritoneal/pelvis drainage. Avoidance of systematic use of the resection site drainage is therefore recommended. In RC, no specific data are available, but due to the ureteroileal anastomosis and extended lymph node dissection, drainage may be useful to diagnose urinary leakage. Drainage avoidance cannot be formulated based on the available data [15].

Antimicrobial Prophylaxis and Skin Preparation

Aerobes and anaerobes bacteria should be covered due to intestinal interruption. As RC is considered as a "clean-contaminated" surgery, a single perioperative course of a second- or third-generation cephalosporin is recommended [50]. The particular resistance pattern of local common germs should be assessed by an infectious disease specialist to determine an appropriate antibiotic prophylaxis regimen. Prolonged (>24 hour) antibiotic prophylaxis may increase the risk for hospital acquired *Clostridium difficile* infection [51].

Standard Anesthetic Protocol

Given the absence of specific studies investigating the role of different anesthetic regiment applied to RC, we recommend to follow the ERAS® Society consensus statement for gastrointestinal surgery [13, 15, 52].

Perioperative Fluid Management

Fluid management has evolved substantially since the introduction 20 years ago of dynamic parameters (systolic pressure or pulse pressure variation) indicating fluid responsiveness and driving anesthesiologists' decisions. Initially, liberal fluid therapy went along with significant weight gain following surgery, and more restrictive regimens have been postulated, although there is no clear definition to date [53]. Despite heterogeneous studies, goal-directed fluid therapy (GDFT), based on minimal fluid administration for dynamic parameters maintenance, appears to decrease surgical morbidity and postoperative complications, reducing the need for postoperative intensive care [54]. Lack or excess of fluid may lead to a paralytic ileus, which is considered one of the major concerns for early recovery. Consequently, a so-called zero fluid balance strategy has been contemplated as an optimal perioperative fluid management [55].

In RC, norepinephrine combined with restrictive fluid administration showed improved surgical outcomes [56, 57]. The use of esophageal Doppler during the intervention has optimized intraoperative fluid management. Near-maximal stroke volume showed a decreased ileus rate, probably due to better cardiac output optimization, particularly in the first operative hour [58]. Interestingly, this strategy has shown no advantages when applied to colorectal surgery [59].

Restrictive fluid management has been quite challenged lately as GDFT benefit appears attenuated by the ERAS recovery protocol in major abdominal surgeries [60, 61]. Recent prospective studies did not link an increased complication rate with increased intraoperative IV fluid intake in patients undergoing RC [62]. Moreover, a potential increased risk of acute kidney injury has been found when restrictive fluid management is applied in major abdominal surgery [63]. Despite the ERAS subgroup analysis of the Myles study confirming these results in the urological population [64], prospective study is mandatory to assess different fluid regimens in an ERAS protocol applied to RC/nephrectomy patients to elude this ongoing controversy.

Preventing Intraoperative Hypothermia

Maintaining constant body temperature during major surgery appears to be critical as it has been demonstrated that hypothermia increases postoperative complications in colorectal surgery [13]. Preoperatively debuted forced-air warming with intraoperative monitoring seems to be the most effective and convenient strategy, especially in vulnerable patients [65].

The Postoperative Phase

Nasogastric Intubation

In RC, nasogastric intubation (NGI) seems to have no benefit [66–70]. A Cochrane meta-analysis evaluating the impact of NGI in major abdominal surgery showed an increased rate of complications, especially pulmonary, and no advantages. Routine use of prolonged NGI can therefore be safely avoided [71].

Urinary Drainage

Ureteroileal anastomosis stenting (UAS) seems to reduce postoperative upper tract dilatation and the risk of metabolic acidosis in RC, regardless of the type of urinary derivation [72]. Moreover, patients with a perioperative stenting may significantly improve recovery of bowel function compared to those without a stent. UAS may have no impact on the risk of early postoperative stricture. No specific study assessed the appropriate duration of UAS.

Prevention of Prolonged Postoperative Ileus

Prolonged postoperative ileus (PPOI) is a major challenge for early discharge of RC patients and a key feature in the ERAS protocol. It has been estimated that more than 50% of patients will be diagnosed with PPOI during the postoperative phase after RC [58]. The consensus on the definition of PPOI is lacking and ranges from clinical ileus on postoperative day 4 to reinsertion of nasogastric tube [73]. Identified risk factors are age, male gender, low preoperative albumin, opioid use, previous abdominal surgery, long operative time, and blood loss [74]. ERAS patients seem to have lower PPOI rates following RC when compared to those treated with traditional postoperative care [75, 76].

PPOI prevention is a key step. Intraoperative fluid management (splanchnic hypoperfusion/salt and fluid overload), minimally invasive surgery (reduced bowel handling, trauma and inflammation) and ureteral stenting showed earlier bowel recovery [72, 74, 77]. In the postoperative phase, prokinetic agents such as metoclopramide and dexamethasone prevent nausea and vomiting but may not have an impact on bowel recovery. No benefit on time to flatus and oral intake tolerance was observed when erythromycin was administered. On the other hand, use of laxatives may be beneficial. Nonsteroidal anti-inflammatory drugs (NSAIDs) may be a valid alternative to opioid-sparing strategy, but there are some concerns about anastomosis healing impairment.

Following the same trend, TEA showed reduction of PPOI after major open surgery compared to systemic opioid [78]. Magnesium sulfate also showed decreased need for opioid consumption and PPOI reduction in gastrointestinal surgery [79]. Early oral nutrition showed LOS and complication rate reduction in colorectal surgery but no impact on the risk of nasogastric tube reinsertion [80]. A large Cochrane review confirmed the benefit of chewing gum to enhance bowel recovery [81]. In RC, significantly decreased time to first flatus and bowel movement was observed [82, 83].

Alvimopan is a peripherally acting μ(mu)-opioid receptor antagonist showing very interesting results in prevent-

ing PPOI. μ(mu)-opioid receptors are largely present in the gut, and Alvimopan has limited passage to the central nervous system, preserving analgesic effect of systemic opioid drugs. Since its approval by the US Food and Drug Administration (FDA) in 2013 for primary bowel anastomosis surgery, a few randomized clinical trials have shown it could reduce the incidence of PPOI and nasogastric tube reinsertion in RC patients [84–87]. However, potential increased cardiovascular events are related to Alvimopan. Finally, cost-effectiveness analysis reports a modest but significant benefit [88].

Prevention of Postoperative Nausea and Vomiting

A multimodal approach is recommended to prevent postoperative nausea and vomiting (PONV). A combination of anesthetic gas and opioid use contributes to PONV, and female patients, history of PONV/motion sickness, nonsmokers, and chronic opioid users have higher risk [9]. Perioperative fluid optimization and UAS seem to reduce PONV [58, 72].

Postoperative Analgesia

Opioid use and abuse is a serious public health concern, especially in the United States where opioids misuse has led to a public health crisis [89]. Pain management and opioid-sparing strategies are two ERAS protocol's cornerstones [13]. The ERAS opioid-sparing protocol seems to reduce PPOI and LOS [90].

Use of para-incisional subfascial catheters is gaining more importance as part of opioid-sparing strategies. A recent meta-analysis including 2059 patients has demonstrated the effectiveness, reliability, and cost effectiveness of continuous wound infiltration (CWI) [91]. Better recovery parameters, less opioid consumption, reduced incidence of hypotension, and even patient satisfaction seemed to advocate the use of preperitoneal CWI. These results are of particular interest when dealing with ERAS [92, 93].

To the best of our knowledge, there is to date no specific study for urological procedures, but given some evident similarities with abdominal surgery, benefits could be expected. In laparoscopic RP, paracetamol/NSAID combined with transversus abdominis plane block showed good analgesic effect and may potentially lead to an "opioid-free" pain control [94, 95].

Early Mobilization

Although no specific study to date has demonstrated an association with improved postoperative outcomes and early mobilization, bed rest promotes thromboembolic, musculoskeletal, and pulmonary complications [96]. In RC and RP patients, LOS and readmission rate may be reduced when early mobilization is implemented as part of the ERAS protocol [66, 75, 97, 98]. A structured mobilization plan and multidisciplinary approach are crucial [99].

Early Oral Diet

In the ERAS protocol, avoiding postoperative starvation seems to be a key step to improve postoperative outcomes. Catabolic state and insulin resistance induced by fasting lead to poor wound healing and amplified postoperative stress [100]. In urological surgery, early oral diet is increasingly adopted. In a recent series, higher infectious complication rates and no improvement on LOS and return to gastrointestinal functions have been reported when total parenteral nutrition was used [101].

No specific study has been designed on RC patients. In colorectal surgery, the rate of wound infection, intra-abdominal abscess, or anastomotic leak was not increased when early enteral feeding was used [102, 103]. Therefore, a fast return to normal oral diet should be reached, avoiding prolonged fasting after RC.

Audit

In healthcare, audit and feedback lead to small but potentially important quality improvement, in particular when baseline adherence to available protocols is low [104]. One strength of the ERAS protocol is the implementation of a dedicated auditing system, ERAS® Interactive Audit System (EIAS® – Encare AB, Stockholm, Sweden), although compliance assessment seems to be critical when ERAS is implemented at the beginning [103]. A recently published retrospective study showed an association between high adherence to ERAS protocol (i.e., >70%) and improved 5-year cancer-specific survival after colorectal cancer surgery [104].

Do Guidelines Really Work? Clinical Results in the "After Guidelines" Era (2014–2018)

Before the publication of the first ERAS guidelines for RC in 2013, other's ERAS protocols were applied to urological patients. However, the compliance was low/not reported and far from a so-called full ERAS protocol, including all 20 or so items recommended by the ERAS Society guidelines. The definition of specific guidelines for RC improved the compliance to the protocol.

In a recent meta-analysis on the impact of ERAS on RC patients' recovery [11], implementation of a standardized pathway clearly improves early discharge and bowel function and reduces postoperative complications.

After urologic ERAS guidelines publications, reported compliance to ERAS items is increasing in published studies.

Daneshmand et al. followed 17 ERAS items with a LOS reduced from 8 to 4 days without affecting complication or readmission rates [105]. To achieve these outstanding results, specific items such as home IV hydration and use of Alvimopan were added to the protocol. In many European countries, patients would be reluctant to be discharged home with equipment such as IV hydration, which makes these results hardly reproducible due to each population's culture and healthcare system differences.

Since high adherence to ERAS protocol seems to be linked with better outcomes, as shown before, an important remark has to be made. In a recent survey, 68% of surgeons identify themselves as "ERAS-surgeons" when only a fifth endorsed all the 11 ERAS core principles [106]. Lack of convincing evidence and the belief that a full ERAS protocol does not improve recovery were the two main reasons for nonadherence to ERAS.

The ERAS concept is built to evolve constantly, through internal audit of quality and outcomes in implemented centers, but also by pooling the collected results to permanently challenge the best practices. To reach this goal, multicentric, prospective, powerful studies are needed, taking into account urological specificities.

Urological Specific Highlights

Although ERAS guidelines on open RC have been built based on the colorectal experience, some important points remain to be addressed. Despite optimized and standardized pathways, RC remains a surgical intervention with high risk of morbidity. Indeed, even when performed in a high-volume center, 50–60% of patients will have some kind of postoperative complications [105]. As pinpointed by Danna et al., multiple factors can contribute to high complication rates and impair optimal recovery [107]. Patients who suffered from muscle invasive bladder cancer are often elderly with poorer health status. Furthermore, RC is a complex and challenging surgical procedure per se with extensive lymphadenectomy, digestive anastomosis, and a prolonged reconstructive phase in case of urinary diversion. In contrast to colonic surgery, a minimally invasive technique is not prerequisite since there is no robust data showing a significant benefit in case of RC. Moreover, the use of intraabdominal drainage, ureteral stents, and transurethral catheters can be useful in urological surgeries even if an ERAS mindset tends to avoid it. Indeed, drainage and catheterization are often responsible for low compliance rates. This has to be kept in mind when performing benchmarking and studies.

RP remains to date one of the primary therapeutic options for localized prostate cancer and represents one of the most extensively performed urological procedures worldwide. To date, few data are available on the impact of ERAS for RP in the literature. Abou-Haidar et al. showed a reduction of LOS from 3 to 2 days without increasing complications rates or hospital readmissions, regardless of the surgical approach [108]. The trend toward robot-assisted RP (RARP) has decreased the average LOS significantly worldwide. Whether there could be an added benefit of ERAS protocols in reducing LOS, which is usually between 1 and 3 days after RARP, can be questioned [109]. We believe that classical endpoints such as LOS or complications rate might not be well suited for RARP [110]. Other endpoints such as cost-effectiveness, patient satisfaction, and cancer-specific survival should definitely be evaluated in randomized clinical trials and could be positively influenced by ERAS pathways. As for RC, a prehabilitation program for RARP is feasible and safe and leads to increased physical and psychological well-being [111].

Similar conclusions can be drawn for radical nephrectomy. Several studies report a LOS reduction ranging from 40% to 50% in open surgery if ERAS principles were applied [112, 113]. Since the dissemination of minimally invasive techniques from the 1990s, LOS, pain control and complication rates have been improved dramatically [114, 115], despite heterogeneity in the studied populations (living kidney donors, small or large renal mass). Therefore, for this type of procedure, the potential of an ERAS protocol might be reduced.

Conclusion and Future

ERAS principles allowed for a change in paradigm. This multidisciplinary approach based on available and acquired evidence has succeeded in reducing LOS, complication rates, and aided bowel recovery in many studies involving RC patients. Considering the optimization of the perioperative phase rather than focusing all efforts on the operative period has allowed for clinical outcomes improvements. While the interest for ERAS has grown in the urological community lately, there is still a lack of evidence and awareness worldwide. We strongly believe that clinical pathway standardization, communication, benchmarking, and strict scientific evaluation of new strategies and technologies will help improve patient outcomes. In our opinion, this will only be achieved if multidisciplinary and multi-institutional efforts are undertaken. Finally, aiming for the development of a standardized ERAS protocol, most studies were designed to evaluate immediate to short-term outcomes such as morbidity, 30-day mortality, or LOS. Longer-term outcomes such as 90-day morbidity, patient's satisfaction, and overall or cancer-specific survival should be considered for future studies.

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ERAS for Breast Reconstruction

45

Claire Temple-Oberle and Carmen Webb

What Is Breast Reconstruction?

Breast reconstruction encompasses a wide range of procedures that can be done at the time of mastectomy (immediate) or at a later date once oncologic care is complete (delayed). Breast reconstruction may involve the use of implants (alloplastic reconstruction), a patient's own tissue called a "flap" (autologous reconstruction), or a combination of an implant and a flap. Breast reconstruction is rarely a single operation—it commonly involves multiple surgeries over time as planned or unplanned procedures [1].

Why Do Women Choose Reconstruction?

Each woman's decision is based on unique factors personal to her health and situation. Women's reasons for undergoing breast reconstruction vary and may include easing clothing fitting challenges, avoiding an uncomfortable or inconvenient prosthesis, feeling "whole" or "normal," and averting a constant reminder of breast cancer [2]. Some women describe restoration of self-image, femininity [3], and other improvements of quality of life [4].

Breast reconstruction is an elective procedure, and not all women interested in reconstruction undergo it. Some women have cancer factors that preclude reconstruction in the immediate setting, such as an anticipated need for radiation after mastectomy. Some women have health issues, such as multiple comorbidities that preclude reconstruction even in the delayed setting [5]. A patient may view the projected aesthetic and functional results and feel these results may not justify the risk of complications that may occur. Risks can vary from trivial to severe but occur relatively frequently [6].

When considering reconstruction, it must be remembered that the cancer treatment comes first, including ablative surgery and any neoadjuvant or adjuvant therapies required. In early-stage breast cancer, reconstruction can often be done in the immediate setting with a low likelihood of delaying cancer therapy [7]. However, in more advanced situations, it is best to allay the risk associated with reconstruction and proceed at a later date when a woman's oncologic care is complete. Often multidisciplinary discussions are required to optimize the timing of reconstruction.

What Types of Breast Reconstruction Are Available?

Alloplastic breast reconstruction generally involves initial placement of a temporary tissue expander under the chest musculature [8]. The device is inflated over weeks to months, and once the soft tissues are suitably stretched, the expander is removed and replaced with a permanent implant. At this second procedure, it is not unusual to have a balancing breast augmentation, reduction, or lift to try to symmetrize the contralateral breast [9]. Another option for implant reconstruction is a direct-to-implant single-stage approach that can be used in the setting of immediate breast reconstruction (Fig. 45.1) [10]. An acellular dermal matrix is generally used in this situation to effectively lengthen the pectoralis major muscle in lieu of the tissue expansion process [11]. The appeal of a single-stage reconstruction must be weighed against an increase in complications [12]. An even newer technique is a pre-pectoral implant placement under a large piece of acellular dermal matrix [13]. These direct-to-implant techniques hinge on tissue perfusion assessment to minimize necrosis complications [14, 15].

Autologous breast reconstruction involves fashioning a new breast from tissue harvested and transplanted from a distant part of the woman's body. A common autologous reconstructive option is to use an abdominal flap based on

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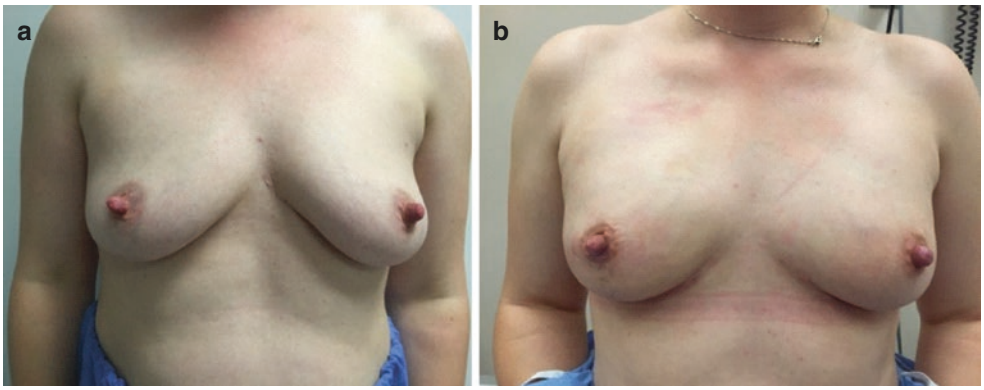

Fig. 45.1 This patient has a genetic predisposition for breast cancer. (**a**) Preoperative photo prior to immediate bilateral nipple-sparing mastectomies and direct-to-implant reconstruction with acellular dermal matrix. (**b**) Postoperative results

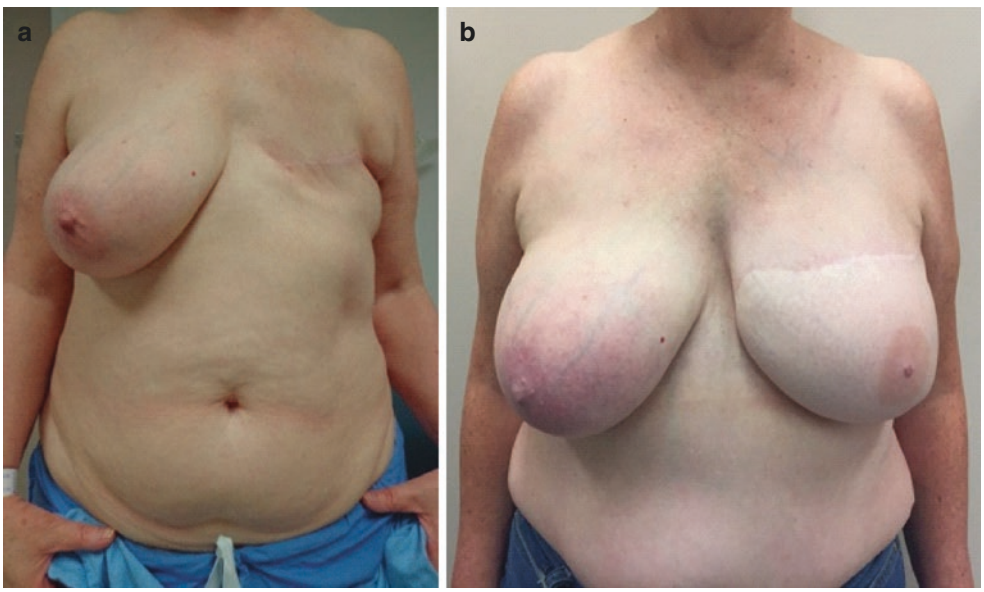

Fig. 45.2 This patient has had a previous left modified radical mastectomy for breast cancer. (**a**) Preoperative photo prior to delayed reconstruction with a deep inferior epigastric artery perforator (DIEP) flap. (**b**) Postoperative results

the circulation from the deep inferior epigastric artery (DIEA). Common variants of these flaps include the TRAM (transverse abdominis myocutaneous) flap and the DIEP (deep inferior epigastric artery perforator) flap (Figs. 45.2 and 45.3). The TRAM flap involves resecting the entire rectus abdominis muscle to perfuse the overlying lower abdominal pannus, while the DIEP involves dissecting within, yet preserving the rectus abdominis muscle and retrieving small perforating branches of the vascular system in continuity with the main pedicle. Both of these procedures violate the abdominal wall fascia, thus carrying the morbidity of an abdominal and fascial incision with subsequent risk of abdominal wall weakness, bulge or frank hernia, in addition to the morbidity of the breast surgical site [16]. Furthermore, these flaps are often transplanted using microvascular technique, which adds time to the procedure [17] and increases the risk of fluid overload. Overly aggressive fluid resuscitation is a known risk factor for flap failure and other complications after abdominal flap reconstruction [18].

The latissimus dorsi (LD) myocutaneous flap is another common reconstruction option (Fig. 45.4). The LD flap is a shorter operation than an abdominal flap since the circulation remains attached (pedicled) during the transfer of the back tissue to the breast. This flap is often used in combination with an implant to provide increased volume; thus this combination modality carries the risks associated with implants (infection, dehiscence, skin necrosis, capsular contracture, implant rupture) and the consequences of latissimus flap harvest (seroma, partial flap necrosis, shoulder girdle weakness) [19]. A newer technique avoids the prosthesis by lipofilling the pectoralis and latissimus muscle [20]. Other microvascular flap options also exist but are used less commonly, including tissue from the abdomen based on the superficial vascular system (SIEA – superficial inferior epigastric artery flap), tissue from the upper inner thigh (TUG – transverse upper gracilis flap), and tissue from the buttocks (SGAP – superior gluteal artery perforator flap), to name a few.

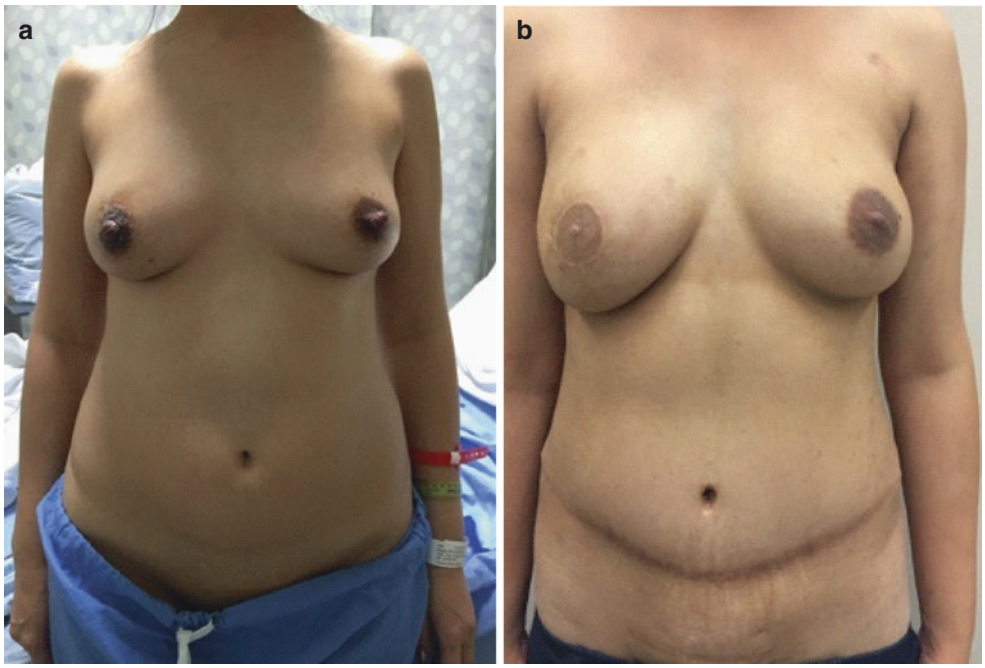

Fig. 45.3 (**a**) This patient is planned for right skin-sparing mastectomy and immediate deep inferior epigastric artery perforator (DIEP) flap breast reconstruction. (**b**) Postoperative result after right nipple reconstruction and areolar tattooing

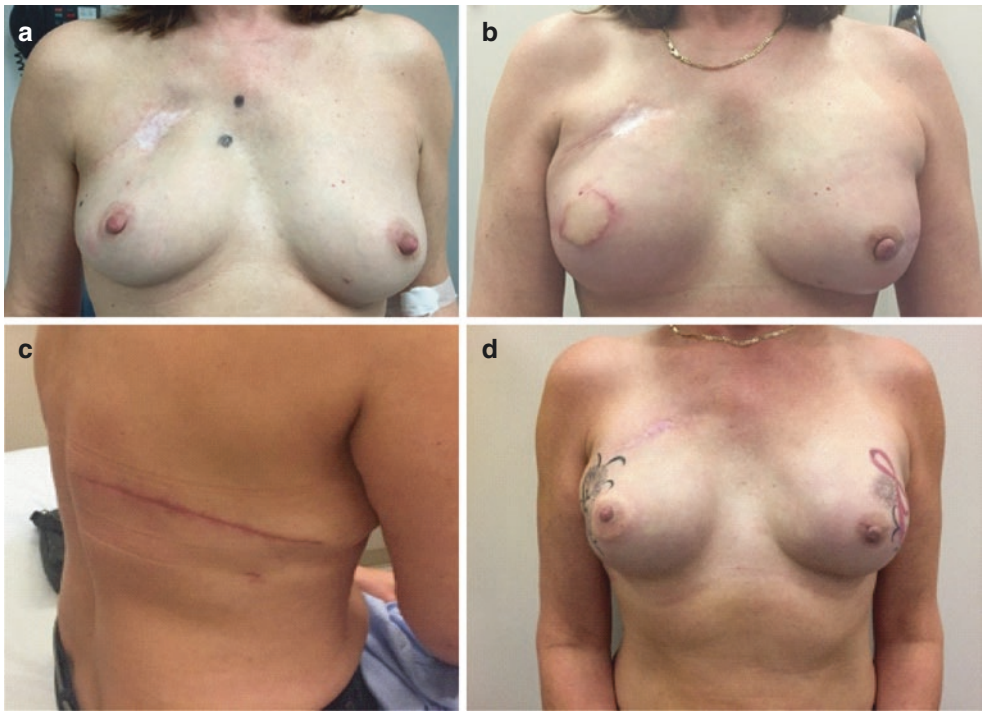

Fig. 45.4 This patient has a recurrent right breast cancer after lumpectomy and radiation. (**a**) Preoperative photo prior to right skin-sparing mastectomy, left prophylactic nipple-sparing mastectomy. (**b**) Early result after immediate right latissimus dorsi (LD) flap and implant, and left direct to implant with an acellular dermal matrix. (**c**) Donor site scar right back. (**d**) Final result after left to right nipple-sharing graft, right areolar tattoo, and scar-camouflaging tattoos

Why Do Women Undergoing Breast Reconstruction Need an Enhanced Recovery After Surgery (ERAS) Pathway?

Recovery Is Unexpectedly Difficult

Women undergoing breast reconstruction report feeling ill-prepared for the unexpectedly challenging recovery process [21]. The unanticipated strain of the recovery process contributes to poorer satisfaction with breast reconstruction outcomes [22]. Recovery scores, as reported on the validated BRECON-31 (breast reconstruction satisfaction questionnaire), are consistently low across a variety of breast reconstructive options when patients are on traditional recovery pathways [23].

Women are Undergoing More Breast Surgery than in the Past

Women with unilateral breast cancer are increasingly choosing bilateral mastectomies for fear of contralateral breast cancer and in a desire for optimal symmetry [24]. Bilateral reconstruction doubles the surgical trauma and stress response and increases operative times [25]. Venous thromboembolism in microvascular breast reconstruction increases with the additional operative time required in bilateral reconstruction [26].

While women are undergoing twice the surgical injury to the chest, there is ever-increasing pressure from institutions to shorten hospital stay. Three decades ago, Canadian women in Alberta undergoing breast cancer surgery were hospitalized on average for 15 days [27]. By the year 2000, this decreased to 2.9 days without increasing complication or readmission rates and maintaining patient satisfaction. By 2013, the combined average length of stay in an Alberta tertiary care hospital for a mastectomy with or without immediate implant-based reconstruction was 2.1 days [28]. In the United States, implant patients are undergoing bilateral mastectomies, node surgery, and bilateral implant breast reconstruction with planned same-day discharge [29]. This has been shown to be safe as long as comorbidities are taken into consideration. In order to facilitate increasingly shorter periods of inpatient care, patients need the kind of careful and comprehensive perioperative care that an enhanced recovery after surgery (ERAS) protocol is designed to provide to ensure their pain, nausea, and vomiting are managed effectively in order to enable an acceptable quality of recovery at home. National and international trends are now moving the standard of care for mastectomies and implant breast reconstructions to the outpatient setting, without negatively impacting complication or readmission rates and maintaining patient satisfaction [30–35].

In the case of abdominal flap patients, these procedures are full-day operations involving both abdominal and breast surgical sites, considerable pain, and risks of deep vein thrombosis (DVT) and pulmonary embolism (PE). These major surgeries benefit from ERAS© for the same reasons that other major abdominal procedures do [36]. A Toronto team implementing an ERAS protocol was able to successfully move their nonmicrovascular abdominal flap reconstruction patients to a single overnight stay [37].

Postoperative Nausea and Vomiting Risk Is Particularly High in This Patient Population

Breast reconstruction patients are at high risk for postoperative nausea and vomiting (PONV) given that they are female, are generally nonsmokers by selection, and are having breast surgery [38].

Breast Reconstruction Is Almost Always a Series of Operations, Resulting in Multiple Recovery Periods

It is rare that breast reconstruction is a single operation. Tissue expanders require a second operation for implant exchange. Direct-to-implant procedures with an acellular dermal matrix often require revision for reasons of asymmetry or changes in volume preference. Abdominal flap procedures occasionally require an emergency take-back for a clotted anastomosis and, in the nonurgent setting, often require surgery for abdominal scar and breast mound revision. For patients with a unilateral reconstruction, there is often an additional surgery for symmetrizing the contralateral healthy breast. Over time, age effects may differ between a reconstructed breast and a natural breast; asymmetry may redevelop, and this may require further surgical revision. Finally, over time implants can degrade and require replacement. These additional procedures can be painful and nausea-inducing, and each carries its own period of recovery. Maximizing each recovery is an important goal in breast reconstruction patients.

What Are the Recommendations in the ERAS© Guideline That Are Unique to Breast Reconstruction?

Experts from Canada, the United States, Brazil, Belgium, and Sweden developed the ERAS® Breast Reconstruction guideline [39]. Eighteen recommendations were developed, many of which are similar to other major surgical guidelines [40]. A few breast-specific guidelines were developed for this unique patient population and are described below. The recommendations, the level of evidence to support the recommendations, and the grade of recommendation are shown in Table 45.1 (see also Fig. 45.5 for general ERAS principles for breast reconstruction).

Preadmission

Preadmission information, education, and counseling are critical in this patient population. In addition to standard ERAS counseling, extensive counseling is required regarding breast reconstruction choices. Specific information regarding type and timing of breast reconstruction, outcomes, and recovery impacts patient satisfaction with her reconstruction [21]. Appropriate preoperative information and a shared decision-making process can maximize satisfaction across a variety of reconstructive options [9]. Preadmission optimization is also important as obesity, smoking, and poorly controlled diabetes are all independently related to complications with breast reconstruction [41]. Given the time-sensitive nature of cancer surgery, full optimization may not be possible.

Table 45.1 ERAS® Society enhanced recovery after surgery recommendations for perioperative care in breast reconstruction

Item	Recommendation	Evidence level	Recommendation grade
1. Preadmission information, education, and counseling	Patients should receive detailed preoperative counseling	Moderate	Strong
2. Preadmission optimization	For daily smokers, 1 month of abstinence before surgery is beneficial	Moderate (smoking)	Strong
	For patients who are obese, weight reduction to achieve a BMI ≤ 30 kg/m^2 before surgery is beneficial	High (obesity)	
	For alcohol abusers, 1 month of abstinence before surgery is beneficial	Low (alcohol)	
	For appropriate groups, referral should be made to resources for these behavior changes		
3. Perforator flap planning	If preoperative perforator mapping is required, CTA is recommended	Moderate	Strong
4. Perioperative fasting	Preoperative fasting should be minimized, and patients should be allowed to drink clear fluids up to 2 hours before surgery	Moderate	Strong
5. Preoperative carbohydrate loading	Preoperative maltodextrin-based drinks should be given to patients 2 hours before surgery	Low	Strong
6. Venous thromboembolism prophylaxis	Patients should be assessed for venous thromboembolism risk. Unless contraindicated and balanced by the risk of bleeding, patients at a higher risk should receive low-molecular-weight heparin or unfractionated heparin until ambulatory or discharged. Mechanical methods should be added	Moderate	Strong
7. Antimicrobial prophylaxis	Chlorhexidine skin preparation should be performed and intravenous antibiotics covering common skin organisms should be given within 1 hour of incision	Moderate	Strong
8. Postoperative nausea and vomiting prophylaxis	Women should receive preoperative and intraoperative medications to mitigate postoperative nausea and vomiting	Moderate	Strong
9. Preoperative and intraoperative analgesia	Women should receive multimodal analgesia to mitigate pain	Moderate	Strong
10. Standard anesthetic protocol	General anesthesia with TIVA is recommended	Moderate	Strong
11. Preventing intraoperative hypothermia	Preoperative and intraoperative measures, such as forced air, to prevent hypothermia should be instituted. Temperature monitoring is required to ensure the patient's body temperature is maintained above 36 ° C	Moderate	Strong
12. Perioperative intravenous fluid management	Over-resuscitation or under-resuscitation of fluids should be avoided, and water and electrolyte balance should be maintained. Goal-directed therapy is a useful method of achieving these goals. Balanced crystalloid solutions, rather than saline, is recommended. Vasopressors are recommended to support fluid management and do not negatively affect free flaps	Moderate	Strong
13. Postoperative analgesia	Multimodal postoperative pain management regimens are opioid-sparing and should be used	High	Strong
14. Early feeding	Patients should be encouraged to take fluids and food orally as soon as possible, preferably within 24 hours after surgery	Moderate	Strong
15. Postoperative flap monitoring	Flap monitoring within the first 72 hours should occur frequently. Clinical evaluation is sufficient for monitoring, with implantable Doppler devices recommended in cases of buried flaps	Moderate	Strong
16. Postoperative wound management	For incisional closure, conventional sutures are recommended	High (sutures)	Strong
	Complex wounds following skin necrosis are treatable with debridement and negative-pressure wound therapy	Moderate (NPWT)	
17. Early mobilization	Patients should be mobilized within the first 24 hours after surgery	Moderate	Strong
18. Postdischarge home support and physiotherapy	Early physiotherapy, supervised exercise programs, and other supportive care initiatives should be instituted after discharge	Moderate	Strong

Reprinted with permission from Temple-Oberle et al. [39]
BMI body mass index, *CTA* computed tomographic angiography, *TIVA* total intravenous anesthesia, *NPWT* negative-pressure wound therapy

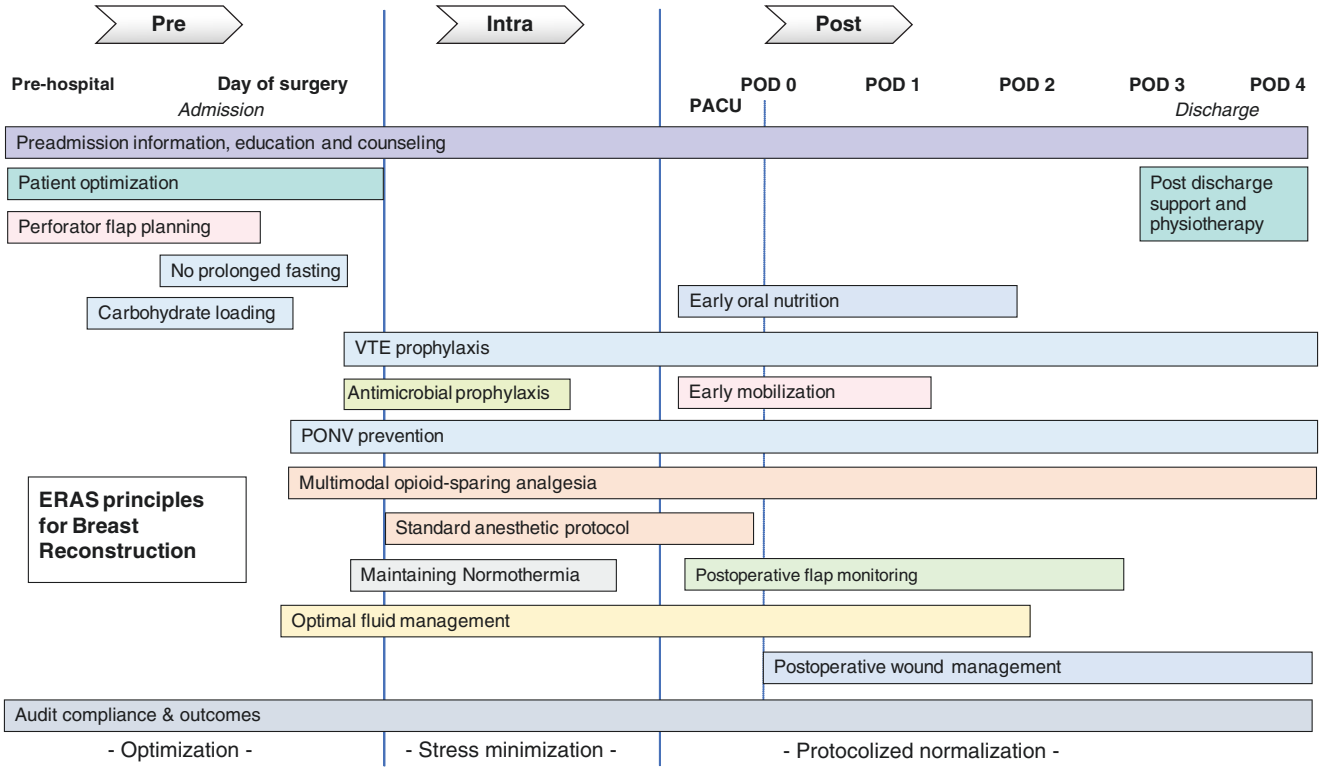

Fig. 45.5 General ERAS principles for breast reconstruction. VTE venous thromboembolism, PONV postoperative nausea and vomiting

Preoperative

Minimizing fasting time and ensuring preoperative carbohydrate loading of breast reconstruction patients align with other ERAS® guidelines, but venous thromboembolism (VTE) prophylaxis bears special mention. The Caprini score is valid in plastic surgery patients [42] and should be applied. Even a seemingly low-risk patient—a 45-year-old woman with early-stage breast cancer undergoing mastectomy and sentinel node biopsy along with a direct-to-implant breast reconstruction—scores reasonably high on the Caprini scale. This patient requires both mechanical and pharmaceutical VTE prophylaxis. Utility of extended pharmaceutical VTE prophylaxis is less well known [43].

Intravenous antibiotics should be given within an hour of skin incision and for 24 hours postoperatively to limit surgical site infection. The usefulness of longer duration of antibiotics is uncertain [44]. Skin preparation solutions should be chlorhexidine based to limit peri-prosthetic breast implant infections [45]. Drains are still commonly used, as seroma formation following mastectomy is ubiquitous [46]. Seromas carry a high risk of surgical site infection and are particularly detrimental to acellular dermal matrix revascularization [47]. Prophylaxis against postoperative nausea and vomiting is critical as these patients carry many risk factors for PONV including female gender, nonsmokers (generally by selection), and having breast surgery [48].

Intraoperative

Multimodal analgesia is a necessity in efforts to minimize opioids. Maintaining normothermia is an element common to all ERAS protocols. Goal-directed fluid resuscitation is important, particularly in long procedures for microvascular breast reconstruction, given the direct correlation of rate of fluid administration and complications in free flap breast reconstruction [18]. Vasopressors are safe in a normovolemic patient undergoing microvascular breast reconstruction [49]. Salt-containing solutions should be minimized. A standard anesthetic protocol, and in particular the use of a total intravenous anesthetic (TIVA), further minimizes PONV. Paravertebral blocks [50] are useful to limit opioids but need to be balanced against the rare risk of pneumothorax that could lead to delay of surgery [51]. There is some controversy whether pectoralis blocks are as safe and effective [52, 53]. The role of transversus abdominis plane (TAP) blocks at the abdominal donor site is less clear in regard to reducing opioid requirements [54]. Ongoing work to ascertain whether regional anesthesia reduces breast cancer

recurrence may further tip the scales toward regional adjuncts in breast reconstructive surgery [55, 56].

Postoperative

Multimodal pain management after surgery is important to continue efforts to minimize opioids. A combination of acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and gabapentin are typically used to minimize the need for narcotics [57]. Patient-controlled anesthesia is avoided as it delays time to ambulation [58]. For microsurgical reconstruction, early identification of perfusion issues is critical to optimize possible flap salvage. Most thromboses occur in the first 72 hours; close monitoring is necessary during this time to intervene with attempted salvage [59]. Traditionally, microvascular surgeons restricted oral intake for the first 24 hours in case of need to return to the operating room. Because this happens infrequently, the recommendation is to progress with oral intake as soon as the patient is able. Early mobilization in the first 24 hours is straightforward for implant patients, but for those with abdominal reconstruction, it can be more challenging. Efforts to ambulate free flap patients are necessary to avoid many complications of bedrest [60]. Wound closure is optimized by standard layered suture closure. Chronic wounds from skin necrosis are best managed by vacuum-assisted closure [61, 62].

Post Discharge

The at-home recovery for patients following breast reconstruction is arduous [63]. Physiotherapy should be arranged to promote early return to baseline function [64]. Post-discharge support including outreach from the physician team is important and improves patient satisfaction [65].

What Has the Research Shown in Terms of Efficacy of ERAS® in Breast Reconstruction?

Autologous Breast Reconstruction

The first reported use of ERAS in pedicled TRAM flap breast reconstruction was in 2013 when Davidge [37] reported the safety of expedited discharge in a retrospective series of patients undergoing pedicled abdominal flap. Forty percent of women achieved discharge in 24 hours. It was noted that early discharge increased as experience with the ERAS protocol grew. In a larger prospective series, Davidge [66] demonstrated good quality of recovery in this ambulatory model of care.

The first report of ERAS in microvascular breast reconstruction was in 2015 when Batdorf [67] demonstrated stable pain scores, reduced narcotic use, and a shorter hospital stay in an ERAS cohort. Bonde [68] found similar results and, after refinement of the protocol, described further reductions in length of stay [69]. Additional investigators including Alfonso [70], Astanehe [71], and Kaoutzanis [72] described similar reductions in opioid use and length of stay. A 2018 systematic review of 9 studies and 1191 patients confirmed decreased length of stay and, particularly relevant in view of the opioid epidemic, decreased opioid consumption [73].

Alloplastic Breast Reconstruction

In 2017, the first report of implant-based reconstruction procedures transitioned to outpatient surgery with an ERAS protocol was published by Dumestre [44]. She demonstrated an improved recovery experience with ERAS compared with traditional hospital stay. Traditionally managed inpatients and ERAS outpatients completed the Quality of Recovery 15 [74], with the ERAS cohort having less nausea, enjoying food more, having less severe pain, and feeling more rested. She also showed the safety of this program in a larger cohort of patients with no increase in complications or emergency room visits, even among those undergoing more extensive surgery such as bilateral mastectomies and immediate implant reconstruction [75]. Chiu [76] confirmed a 23-hour stay ERAS model was successful in women undergoing implant-based breast reconstruction in terms of experiencing less pain, nausea, and vomiting.

What Is the Next Frontier of Breast Reconstruction ERAS?

Consistency

A British team in the optiFLAPP initiative surveyed practitioners in the United Kingdom and showed marked variation in application of ERAS principles to microvascular breast reconstruction patients [77]. An ERAS® interactive audit system has been developed for breast reconstruction to help teams identify areas of non-compliance with ERAS® recommendations and to monitor whether complications can be reduced through compliance with poorly adhered elements. Now that the benefits of ERAS have been shown internationally and across common types of breast reconstruction, team audit and feedback is the next step in improving perioperative care for women.

Better Support at Home

Expedited discharge carries the risk of a woman feeling less cared for after breast surgery. Outpatient breast reconstruction patients on ERAS protocols report feeling as equally supported by hospital staff as traditional inpatients through the use of a simple phone call in the immediate postoperative period [43]. Armstrong [78] demonstrated that in-person visits can be reduced via a smartphone application where the patient has an asynchronous virtual visit at home. Patient-reported satisfaction is high, and the technology is cost-effective [79].

The use of telemedicine applications has an increasing role in healthcare and has been shown to reduce post-discharge anxiety, provide early alerts of potentially problematic postoperative complications, increase patient convenience, and reduce healthcare costs [66, 80]. Technological innovation to alleviate burdens for both the healthcare system and individual patients, including asynchronous digital medical care [81], is essential for healthcare systems to incorporate into the pursuit of quality care and patient safety [82]. Further research into the integration of ERAS and telemedicine for home support is the next frontier of enhanced recovery.

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Gynecologic/Oncology Surgery

46

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Introduction

The evidence for benefit of enhanced recovery after surgery (ERAS) in gastrointestinal (GI) surgery is well-documented [1]. Until recently, however, there was very little published on ERAS in gynecologic surgery [2, 3]. A review of enhanced recovery pathways in gynecologic oncology concluded that it was difficult to compare results among the studies found because of mixed populations and inconsistent enhanced recovery elements. While the protocol elements in the studies appeared to show benefit, the dissimilarities among the protocols demonstrated the need to develop a formalized, evidence-based ERAS guideline for patients undergoing surgery for gynecologic cancer [4].

ERAS Gynecologic/Oncology Guidelines

In March 2014, an international group of experts was assembled with the goal of developing an ERAS guideline for gynecologic/oncology surgery. The authors convened in July 2014 to discuss topics for inclusion. The topic list was based on the ERAS colonic surgery [5] and rectal/pelvic [6] guidelines, which were used as templates. The literature search (1966–2014) used Embase and PubMed to search medical subject headings including "gynecology," "gynecologic oncology," and all preoperative, intraoperative, and postoperative ERAS items. Meta-analyses, systematic reviews, randomized controlled studies, nonrandomized controlled studies, reviews, and case series were considered for each individual topic. The quality of evidence and recommendations was evaluated according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system [7]. The guidelines were eventually published in two parts: the preoperative and intraoperative recommendations in Part I [8] and the postoperative recommendations in Part II [9]. A summary of common guideline components is shown in Table 46.1 (see also Fig. 46.1). For a complete list of components, please refer to the original guidelines [8, 9].

There has been widespread interest in the ERAS gynecologic/oncology guidelines as evidenced by these articles

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Table 46.1 Summary of ERAS gynecologic/oncology guideline components

Preoperative	
Preadmission patient education	Did the patient get specific ERAS information preoperatively? (Yes = compliant)
Avoidance of oral bowel preparation	Did the patient receive oral bowel preparation preoperatively? (No = compliant)
Oral carbohydrate treatment	Was the patient treated with a preoperative carbohydrate-rich drink? (Yes = compliant)
Avoidance of long-acting sedative medication	Did the patient get any long-acting sedative premedication after midnight prior to surgery? (No = compliant)
Thrombosis prophylaxis	Did the patient get thrombosis prophylaxis preoperatively? (Yes = compliant)
Antibiotic prophylaxis before incision	Was antibiotic prophylaxis given before skin incision? (Yes = compliant)
PONV prophylaxis administered	Was PONV prophylaxis given before operation? (Yes = compliant)
Intraoperative	
Avoidance of systemic opioids	Did the patient receive long-acting systemic opioids intraoperatively? (No = compliant)
Upper-body forced-air heating cover used	Was an upper-body forced-air heating cover used during the operation? (Yes = compliant)
Avoidance of nasogastric tube use	Was a nasogastric tube left in place after the operation? (No = compliant)
Avoidance of resection-site drainage	Were abdominal and/or pelvic drains used? (No = compliant)
Postoperative	
Prompt termination of urinary drainage	When was urinary drainage successfully terminated? (removed POD1 = compliant)
Stimulation of gut motility	Was the patient's gut motility stimulated? (laxatives, chewing gum = compliant)
Patient weight recorded POD1	What was patient's weight POD1 (in A.M.)? (weight gain <2 kg = compliant)
Prompt termination of intravenous fluid infusion	When was the intravenous infusion successfully terminated? (on day of operation = compliant)
Postoperative nutrition	Was a regular diet started within the first 24 hours after surgery? (Yes = compliant)
Mobilization at all on day of surgery	Did the patient mobilize at all postoperatively, on day of surgery? (Yes = compliant)

PONV postoperative nausea and vomiting

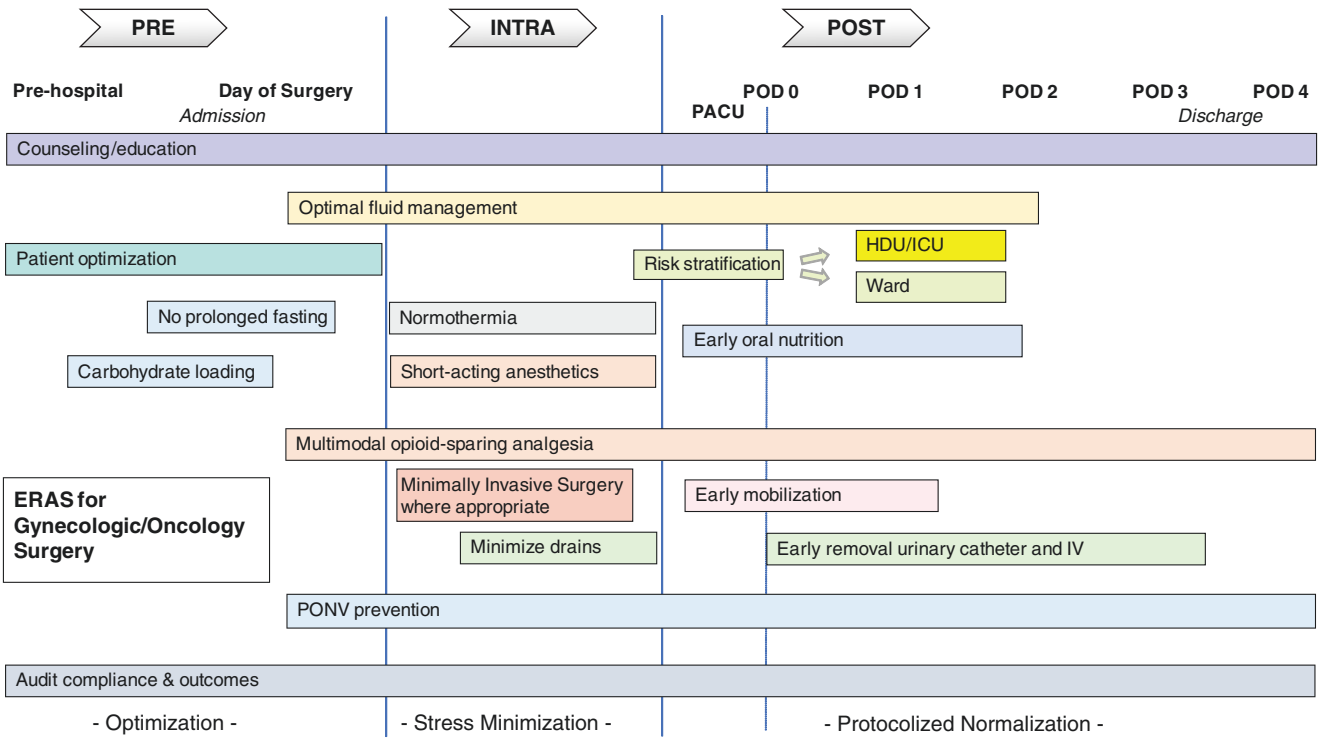

Fig. 46.1 General ERAS principles for gynecologic/oncology surgery. PACU postanesthesia care unit, HDU high-dependency unit, ICU intensive care unit, IV intravenous, PONV postoperative nausea and vomiting

being the most downloaded from the journal *Gynecologic Oncology* (>60,000 downloads as of August 2018). Despite this, many clinical departments still struggle with how to initiate their ERAS program, particularly as it relates to translating the guidelines into an actual protocol. With the goal of addressing this gap, recently Nelson and colleagues published a series of practical recommendations including ERAS order sets and instructions for both ERAS team development and ERAS program audit [10].

The ERAS gynecologic/oncology guidelines have now been translated onto the ERAS Interactive Audit System (EIAS). Bisch et al. were the first to use EIAS for gynecology

and showed that in 519 patients, mean compliance with ERAS care elements increased from 56% to 77% ($p < 0.0001$). Median length of stay (LOS) for all surgeries decreased from 4 days to 3 days post-ERAS ($p < 0.0001$). In medium−/high-complexity surgery, median LOS was reduced by 2 days ($p = 0.0005$). Complications prior to discharge decreased from 53% to 36% post-ERAS ($p = 0.0003$). There was no significant difference in readmissions, complications post-discharge up to 30 days, or mortality between the cohorts. The overall net cost savings to the healthcare system attributable to ERAS implementation was $350,784 with a return on investment (ROI) ratio estimated at 2.1 [11].

Meyer and colleagues compared clinical outcomes among a cohort of 607 women undergoing open gynecologic surgery before and after implementation of ERAS. Median length of stay was reduced by 25% for patients in the ERAS pathway ($p < 0.001$). Overall, patients in the ERAS group had a 72% reduction in median opioid consumption, and 16% were opioid-free during admission up to postoperative day 3 ($p < 0.001$). There were no significant differences in complications, rates of readmission, or reoperation between the pre- and post-ERAS groups [12].

Updates and Areas for Future Inclusion in Guidelines

Since the ERAS gynecologic/oncology guidelines were published, there have been a number of important updates to the field that should be discussed and warrant inclusion in the next version of the guidelines. These updates are highlighted below.

Perioperative Nutritional Care

Multiple randomized studies on early re-feeding have been performed in gynecologic oncology and ovarian cancer [13–18]. The maintenance of an appropriate nutritional status in the postoperative period is recommended and supported [19]. Improvements have included accelerated return of bowel activity, reduced length of stay, and equivalent complication rates related to wound healing, anastomotic leaks, or pulmonary complications [15, 16]. It is important to note that early feeding is associated with a higher rate of nausea, but not vomiting, abdominal distension, or nasogastric tube use, and was defined as intake of fluid or food within 24 hours. Patient satisfaction with control of vomiting in one series was more than 90% with early feeding despite a higher incidence of nausea in the enhanced recovery group [2]. Finally, in colorectal patients, delivery of postoperative nutrition on day 1 is an independent prognostic factor for 5-year survival and mortality [19–21]. Many gynecologic oncology centers have progressed to allow their patients a standard diet during the immediate postoperative period.

Perioperative nutritional supplementation, or immunonutrition, is another emerging area. Current research is examining the roles of polyunsaturated fatty acids, arginine, glutamine, antioxidants, and nucleotides on the effects of inflammation and postoperative healing [19, 22, 23]. Arginine-supplemented diets, which may improve vasodilation and tissue oxygenation, have been examined in a large systematic review and showed a reduction in overall infection (RR = 0.59) and length of hospital stay; there was no difference in mortality [24]. Although most of the included trials were from gastric/colon surgery, one study in gynecologic oncology supported these results [25]. Several large randomized trials in colorectal patients compared an immunonutrition/high-protein feed to a high-calorie supplement and found a lower rate of infection and length of stay in the study group [26, 27]. Currently there are no clear guidelines on protein needs in surgical patients; however, in the acute care setting, guidelines have recommended 2.0 g of protein/kg/day and 25–30 kcal/kg/day [19, 28]. It appears that a high-protein diet postoperatively may reduce complications. The full role of immunonutrition and arginine supplementation continues to evolve.

Venous Thromboembolism Risk in Gynecologic Cancer Surgery

Among patients with cancer, venous thromboembolism (VTE) is the second leading cause of death [29]. The diagnosis of epithelial ovarian cancer (EOC) is an independent predictor of VTE among women undergoing surgery for gynecologic cancer [30]. Recent studies suggest that up to 10% of women with EOC have a clinically evident VTE at the time of their cancer diagnoses, and among women undergoing neoadjuvant chemotherapy for EOC, the risk of VTE is up to 27% during the course of their primary cancer treatment [31]. Among women who undergo primary surgery for EOC, the risk of VTE within the first 30 days after surgery is 7.5% [32] and can reach as high as 42% within the first 6 months of EOC diagnosis [33]. Current recommendations for perioperative VTE prophylaxis in women undergoing surgery for gynecologic cancer follow guidelines outlined by the American College of Chest Physicians (ACCP) [34], American Society of Clinical Oncology (ASCO) [35], and the National Comprehensive Cancer Network (NCCN). All guidelines recommend perioperative dual prophylaxis: mechanical prophylaxis with sequential compression devices and chemical prophylaxis with unfractionated or low-molecular-weight heparin (LMWH). In addition, patients at highest risk for VTE—those who have a score of ≥5 in the Caprini risk assessment model for postoperative VTE [36]—should

receive a daily prophylactic dose of LMWH for a total of 28 days following surgery [34, 35]. The ENOXACAN 2 randomized controlled trial (RCT) provided the Level 1 support of 28 days of prophylactic-dose LMWH, as that trial demonstrated a reduction in postoperative VTE by 60% at both 30 and 90 days in those who received 28 days of LMWH [37].

Women undergoing surgery for gynecologic cancer often fall into the ACCP highest-risk category [34]; however, the Caprini risk assessment was developed based on the risk of VTE in open general surgery [36]. With the advent of minimally invasive surgery in gynecologic cancer care, the generalizability of this risk assessment tool has been questioned, and retrospective data suggests that the risk of VTE following minimally invasive gynecologic cancer surgery is very low and may not warrant extended prophylaxis [38]. However, there are no current guidelines that specifically guide VTE prophylaxis in the setting of minimally invasive surgery.

As patients diagnosed with a solid tumor malignancy often require adjuvant chemotherapy following surgery, the intervention of extended prophylaxis into the adjuvant chemotherapy period has been studied in two placebo-controlled RCTs. In the PROTECHT (PROphylaxis of ThromboEmbolism during CHemoTherapy) trial, patients with solid tumors (lung, breast, gastrointestinal, ovary, head/neck, pancreatic) were randomized 2:1 to prophylactic-dose LMWH vs. placebo while receiving outpatient chemotherapy [39]. While there was a 50% reduction in VTE, the baseline of 4% VTE risk translated to a large number needed to treat among those who met low or intermediate risk for VTE [40] based on their Khorana score [41]. There were similar findings in the SAVE-ONCO RCT of semuloparin vs. placebo during chemotherapy in patients with solid tumors [42]. As such, ASCO and NCCN guidelines do not recommend VTE prophylaxis during ambulatory chemotherapy for solid tumor malignancies [35]. As both the PROTECHT and SAVE-ONCO trials comprised only 12% of ovarian cancers in their patient population [39, 42] and recent data suggests that women with EOC are at a markedly high risk of developing a VTE during the course of their cancer care [31, 33], the baseline risk of VTE may well have been diluted in these large RCTs by the greater proportion of cancer diagnoses that carry lower VTE risks. As such, further prospective trials of VTE prophylaxis, including novel agents such as factor Xa inhibitors, exclusively in woman with active ovarian cancer are currently needed.

Preoperative Bowel Preparation: Current Data and Alternative Approaches

In the 1970s, Nichols and Condon published one of the first reports of a preoperative bowel preparation that combined an oral antibiotic preparation (OAP) with a mechanical bowel preparation (MBP). The potential and perceived benefits included a decrease in the bacterial load within the colon and emptying of the colon, which allowed for better palpation of intraluminal lesions [43]. Since then, the preoperative bowel preparation (OAP + MBP) has been shown to be associated with improvements in surgical site infection (SSI), anastomotic leak, reduction in ileus, and reduction in readmission [44–48]. However, bowel preparation can lead to dehydration, electrolyte abnormalities, and decreased patient satisfaction [49, 50]. With the introduction of ERAS pathways in colorectal surgery, there appeared to be a national swing toward abandoning the bowel preparation in colorectal surgery. However, large studies, including two out of the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) targeted colectomy cohort [47, 51], provided data that has supported the current trend moving back toward bowel preparation in colorectal surgery.

Much of the benefit from bowel preparation is likely derived by the OAP as utilization of an OAP alone appears to improve SSI rates and is associated with a reduction in anastomotic leak. In the most recent ACS-NSQIP study of bowel preparation utilizing the targeted colectomy cohort (nearly 28,000 patients included), organ/space SSI and anastomotic leak reduction were essentially the same whether the preparation utilized was OAP alone or OAP + MBP. There was, however, improved wound dehiscence rate among those who received OAP + MBP, and this was not observed with OAP alone [51]. The addition of MBP is theorized to enhance transit of oral antibiotics through the gastrointestinal tract and may enhance the impact of an OAP.

While the combination of OAP + MBP is associated with decreases in postoperative SSI and anastomotic leak, the utilization of MBP alone can be harmful. Importantly, a MBP typically consists of an orally ingested agent such as an osmotic cathartic (i.e., magnesium citrate), a non-absorbed osmotic (i.e., polyethylene glycol), stimulant laxative (i.e., bisacodyl), or a combination of an osmotic with a laxative [52].There is Level 1 evidence illustrating MBP alone is ineffective in achieving improved postoperative complications and is potentially harmful. A meta-analysis of seven randomized controlled trials of MBP alone vs. no bowel preparation demonstrated there were higher complication rates, including increased rates of anastomotic leak, SSI, and reoperation, observed with MBP alone [53]. Additionally, MBP contributes to preoperative dehydration, decreased exercise capacity, and electrolyte abnormalities [49]. In a systematic review in gynecologic surgery, MBP had no improvement in operative time or surgical field view and led to a more unpleasant patient experience [50]. In the most recent ACS-NSQIP study of bowel preparation, MBP alone had no impact on SSI, wound dehiscence, or anastomotic

leak [51]. As such, the contemporary preoperative bowel preparation should not consist of only a MBP; it should also include an OAP.

While the current data in colorectal surgery may support the utilization of OAP + MBP as a modality to improve certain postoperative outcomes, in gynecologic oncology surgery, the utilization of bowel preparation in the setting of an ERAS program remains controversial. Given the importance of euvolemia in ERAS pathways, dehydration secondary to bowel preparation may counteract some of the beneficial impact of ERAS. Importantly, there is no RCT data comparing OAP alone vs. OAP + MBP, and even among the largest retrospective series reported [51], important counterbalances such as euvolemia and dehydration were not reported. Additionally, there are targeted approaches to mitigate the rates of postoperative complications that have been implemented in the setting of gynecologic oncology surgery ERAS programs with no bowel preparation that have yielded reductions in anastomotic leak, SSI, and ileus.

Complications such as anastomotic leak and SSI are often multifactorial. In the setting of a quality improvement project designed to decrease the rate of anastomotic leak in women undergoing rectosigmoid resection as part of their gynecologic cancer surgery, recognition of the risk factors for anastomotic leak led to the development of a guideline-based approach. Among those who met risk criteria, such as prior pelvic radiation, hypoalbuminemia, and anastomosis ≤6 cm from the anal verge, a protective diverting loop ileostomy was added to their surgical procedure, and this resulted in a reduction of anastomotic leak from 7.8% to 2.6% [54]. Risk factors for SSI include those of host factors, colonization and endogenous flora, surgical procedure variables, as well as surgical team and hospital practice factors. As such, the approach to reducing SSI must be multidimensional. There are several measures that are considered category 1A recommendations by the Centers for Disease Control and Prevention (CDC), including appropriate intravenous antibiotic prophylaxis, skin antisepsis, normothermia, glycemic control, nicotine cessation, and increased oxygenation [55–62]. Additionally, the implementation of SSI reduction bundles, which often include the CDC recommendations, has been shown to decrease SSI in both colorectal surgery and gynecologic cancer surgery with and without a bowel resection [63, 64].

Reducing the rate of ileus also appears to be feasible without a bowel preparation. In a retrospective cohort study, the addition of liposomal bupivacaine to an ERAS protocol led to reduced opioid consumption and reduced ileus by nearly 50% in women undergoing high-complexity ovarian cancer debulking [65]. Additionally, the novel agent alvimopan, which is a peripherally acting, selective, μ(mu)-opioid antagonist, has been shown to decrease ileus-associated morbidity in both colorectal surgery and radical cystectomy by 56% and 72%, respectively [66, 67]. Alvimopan is US Food and Drug Administration (FDA) approved for ileus prophylaxis in patients undergoing a planned large or small bowel resection. In an RCT of alvimopan vs. placebo, alvimopan decreased the rate of ileus following ovarian cancer surgery by 70% [68].

In summary, the utilization of preoperative bowel preparation remains controversial. The beneficial component to the preparation is likely the OAP; however, there is no Level 1 evidence comparing OAP alone vs. OAP + MBP. There is Level 1 evidence demonstrating that MBP alone is harmful. As such, if a bowel preparation is incorporated into perioperative care, OAP + MBP appears to carry the most benefit. However, the benefits long perceived and shown to be achieved with bowel preparation, such as reduced rates of SSI, anastomotic leak, and ileus, can be achieved without the side effects of bowel preparation. Even in the highest complexity gynecologic cancer surgeries, these complications can be greatly reduced through alternative approaches of risk-based guideline utilization, bundled interventions, and novel agents.

Multimodal Pain Control: Strategy to Reduce Postoperative Opioid Consumption

Achieving satisfactory postsurgical pain control is among the top concerns of most patients before and after surgery. The use of minimally invasive approaches—such as laparoscopic, vaginal, and robotic surgery—significantly reduces pain and is one of many reasons these approaches should be utilized before laparotomy when possible. While opioids are likely to continue to be an important aspect of multimodal pain control, the ongoing opioid crisis in the United States has highlighted the importance of using the minimal amount of opioid to minimize the risk of dependence and diversion. In this way, postoperative pain endpoints should include not only reducing pain scores but restoring function with the least amount of opioid possible, including minimizing the use of patient-controlled analgesia (PCA). While some have advocated for the total abandonment of opioids in the perioperative setting, this may not be an achievable or even desirable goal for all patients.

Strategies for achieving satisfactory pain control with the least amount of opioid possible include the use of synergistic non-opioid alternatives, local injection, and regional analgesia. These options are particularly important for patients who are not opioid-naïve prior to surgery. The most well-known form of multimodal analgesia is the use of nonsteroidal anti-inflammatory drugs (NSAIDs) with acetaminophen and has been shown to be superior to the use of either drug alone [69]. Similarly, the combination of oral acetaminophen and cyclooxygenase (COX)-2 inhibitors (celecoxib or parecoxib)

is commonly employed as preemptive analgesia together with gabapentin in many enhanced recovery pathways [2, 70]. Other adjuncts such as intravenous (IV) lidocaine, clonidine, magnesium, and dexamethasone may also be effective in reducing opioid requirements, nausea and vomiting, and inflammation—although the optimal timing, dosage, and potential risks remain to be defined [71–74].

The use of thoracic or lumbar epidural analgesia is effective in controlling postsurgical pain, reducing opioid requirements, and may speed recovery of GI function [75, 76]. However, recent investigations have cast doubt on its efficacy compared to multimodal oral regimens in addition to potential side effects. Controlling pain is ideally accomplished without interfering with regaining function, including ambulation, which may be delayed in patients with epidurals. Up to 30% of epidurals may not be functional, and many patients will nevertheless require a PCA [77]. Furthermore, epidurals are frequently associated with intraoperative hypotension, which often requires fluid boluses and will interfere with the goal of euvolemia, and many will nevertheless require systemic opioids [78].

Local injections into the wound or as TAP (transversus abdominis plane) blocks may be particularly effective when used in combination with multimodal oral pain regimens. While a randomized trial did not show that TAP blocks were more effective than incisional injection, some continue to advocate for this approach [79]. Both interventions have minimal side effects and may offer sustained efficacy when long-acting forms of anesthetic are used, such as liposomal bupivacaine; such injections should be strongly considered for opioid-tolerant patients. In one investigation the use of incisional injection with liposomal bupivacaine reduced the rate of PCA use below 5% when combined with an oral multimodal regimen for patients undergoing complex cytoreduction for ovarian cancer [65].

Total Intravenous Anesthesia (TIVA)

There is an emerging trend toward the use of total intravenous anesthesia (TIVA) for gynecologic oncology surgery within an ERAS pathway. The use of TIVA allows the anesthesiologist to achieve certain intraoperative goals in the pathway, such as rapid awakening in combination with opioid-sparing multimodal analgesia and reduction in postoperative nausea and vomiting (PONV). In addition, potential benefits were described by Wigmore and colleagues when they looked at overall long-term survival for patients undergoing volatile versus IV anesthesia for all cancer surgical procedures. This retrospective analysis demonstrates an association between the type of anesthetic delivered and survival. Mortality was approximately 50% greater with volatile than with IV anesthesia, with an adjusted hazard ratio of 1.46 (1.29–1.66) [80]. Several intravenous anesthetic agents may be used in combination to execute an effective TIVA regimen. Propofol (considered the model drug for TIVA) along with several adjuncts such as dexmedetomidine, ketamine, and lidocaine is used in order to avoid routine use of opioids.

Propofol remains the mainstay drug for TIVA. In addition to its favorable pharmacodynamics and pharmacokinetic profile, propofol offers distinct benefits over inhaled anesthetics. Studies of propofol have shown advantages: Propofol reduced coughing during emergence from anesthesia [81] and the depression in bronchial mucus transport velocity associated with general anesthesia [82]. In addition, the stress hormone response [83] and the expression of pro-inflammatory cytokines in alveolar macrophages [84] were lower in patients receiving propofol than in those receiving inhaled anesthetics. It is also known that propofol serves as a volatile anesthetic-sparing technique for patients with a history of PONV.

Dexmedetomidine is an alpha-2 agonist sedative-analgesic that inhibits endogenous norepinephrine release. Dexmedetomidine is eight times more selective for the alpha-2 receptor than clonidine, with an alpha-2/alpha-1 receptor ratio of 1600:1 [85]. Evidence suggests that its main effector sites are the locus coeruleus for sedative action and the spinal cord for analgesic action. Interestingly, sedation with dexmedetomidine has been observed to mimic natural sleep in that hypercapnic arousal phenomenon upon exposure to a CO_2 challenge is preserved [86]. In addition to its direct sedative-analgesic properties, dexmedetomidine also reduces opioid requirements [87–94] and minimum alveolar concentration levels for inhalational anesthetics [95–97].

Ketamine is an N-methyl-o-aspartate receptor antagonist that induces a "dissociative state" in which sensory input (sight, hearing, touch) normally perceived by the patient is blocked from reaching consciousness. Because of its profound analgesic, sedative, and amnestic properties, it is occasionally used as an adjunct to propofol in TIVA regimens. Ketamine is particularly valuable because it has bronchodilating properties, does not depress respiration, may reduce pain postoperatively, reduces narcotic requirement, and exerts sympathomimetic effects. There is potential for ketamine to have benefits in reducing chronic postoperative pain, but the optimum treatment duration and dose for different operations have yet to be identified [98].

Intravenous lidocaine has also been described as an adjuvant in TIVA. It has been described as having analgesic, antihyperalgesic, and anti-inflammatory properties. The mechanism of action and mechanism of analgesia of intravenous lidocaine reveal its potential advantages in TIVA. Intravenous lidocaine infusion in the perioperative period is safe and has clear advantages, such as decreased intraoperative anesthetic requirements, lower pain scores,

reduced postoperative analgesic requirements, as well as faster return of bowel function and decreased length of hospital stay [99–106]. The final analgesic action of intravenous lidocaine is a reflection of its multifactorial action. It has been suggested that its central sensitization is secondary to a peripheral anti-hyperalgesic action on somatic pain and central on neuropathic pain, which results in the blockade of central hyper-excitability.

Traditionally, TIVA has been administered through calculator pumps that deliver a preset dose per unit of time. Dosages are based on recommended minimum infusion rates that are determined based on age and weight and titrated to clinical effect through measurement of hemodynamics and subjective patient assessment. However, intravenous agents have a narrow therapeutic window that may be difficult to target and maintain [107]. Therefore, computer-controlled IV drug delivery systems, or target-controlled infusion (TCI) systems, have been developed to address the shortcomings of traditional calculator pumps and mimic the convenience, advantages, and familiarity of vaporizers [108]. TCI systems administer intravenous anesthesia based on real-time pharmacokinetic models, derived from population studies specific for each intravenous agent. Although TCI systems are widely available throughout the world (in at least 96 countries), they have yet to be introduced commercially in the United States. Because TCI systems inherently fuse drug and device, the FDA is uncertain whether to regulate TCI as a drug or a device and has stalled TCI system approval; this regulatory roadblock has, unfortunately, hindered commercial interest in furthering TCI technology for the US market [108–110].

Anesthetic depth monitors analyze and process a patient's spontaneous electroencephalogram (EEG) and/or mid-latency auditory-evoked potentials (MLAEP) to gauge hypnotic depth [111]. To date, however, studies have failed to show that anesthetic depth monitors are consistently capable of either detecting intraoperative awareness or distinguishing between consciousness states [112]. However, an increased risk of intraoperative recall in TIVA has never been documented using the Brice interview [113].

In summary, the TIVA technique for gynecologic oncological procedures is a balanced technique, which allows for reduced dosages of medications and opioid sparing.

Goal-Directed Fluid Therapy (GDFT)

Hypovolemia with subsequent tissue hypoperfusion might occur during and after high-risk surgery. Hypovolemia, if undetected, may lead to postoperative complications, including organ dysfunction, prolonged hospital stay, and increased mortality [114–116]. The outcome of patients undergoing high-risk surgery improves by intraoperative fluid management using goal-directed stroke volume (SV) optimization [117–122]. Two meta-analyses demonstrated that intraoperative hemodynamic optimization is effective in reducing both postoperative complications and mortality [123] and postoperative infections [124]. In addition, postoperative organ dysfunction including gastrointestinal complications [122, 125] and renal impairment [126] can be reduced by a goal-directed approach. Since studies aiming at maximizing physiological variables (e.g., cardiac output, oxygen delivery, mixed venous oxygen saturation) had inconsistent results [127–130], a more individualized approach has been advocated [122]. Hypovolemia is the major reason for hemodynamic instability in the perioperative setting [131]. On the other hand, there is evidence that volume excess may also be dangerous [132]. Volume administration is required and is achieved by using dynamic variables, stroke volume variation (SVV), pulse pressure variation, or systolic pressure variation [133]. Fluid optimization guided by SVV is associated with hemodynamic stability and decreased lactate levels as well as reduced postoperative organ complications [134].

For high-risk surgical patients, goal-directed fluid therapy (GDFT)—a technique used to manipulate hemodynamics with the use of fluids and inotropes to improve tissue perfusion and oxygenation—has been associated with improvements in short- and long-term outcomes [135, 136].

One of the key components of an ERAS program in the intraoperative period is the use of GDFT to optimize end organ tissue perfusion [137, 138]. The impact of GDFT in ERAS pathways is much different when compared to the period prior to implementation of such programs. ERAS patients are well-optimized, not exposed to prolonged periods of fasting, or mechanical bowel preparations, and, in addition, are given carbohydrate-loading solutions allowing for better hydration, euvolemia, and less hypotension during induction of anesthesia.

There is limited evidence that GDFT poses significant risk, and the use of advanced hemodynamic monitoring equipment may enhance clinical decision-making when compared with the use of conventional monitors [138]. Several investigators have examined device-guided GDFT in ERAS programs. Three groups independently tested a "zero balance" or "restrictive" strategy against conventional minimally invasive cardiac output monitoring-guided GDFT within the context of colorectal ERAS programs, and all found no difference in the length of stay or incident complications (335 total patients). None of these studies demonstrated adverse outcomes from the use of GDFT [138–141].

Intraoperative GDFT data suggests either a reduction in length of stay or complications; and also because most devices used for GDFT present minimal risk to the patient, GDFT should be implemented when available. Depending on patient- and procedure-specific risks, clinicians may utilize

conventional monitors or minimally and noninvasive cardiac output monitoring devices [138].

Recently Lasala and colleagues investigated the incidence of acute kidney injury (AKI) using the RIFLE criteria (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) in 582 gynecologic oncologic patients undergoing elective surgery within a fully developed ERAS program compared to 74 pre-ERAS patients. The incidence of AKI was 9.6% for the ERAS group and 9.5% for the non-ERAS group. Patients in the ERAS group received less fluids ($p < 0.0062$) and less blood products ($p < 0.0028$). They concluded that the implementation of GDFT within an ERAS program in gynecologic oncology did not result in an increased rate of AKI and was not harmful [142]. A recent study in major abdominal surgery has shown some adverse effects of restrictive fluids regarding AKI among patients at increased risk for complications [143]. It has been widely debated, as the results from this study differ from others [144–146]. Of note, this study was not run according to ERAS standard of care. The actual paradigm of ERAS perioperative fluid therapy advocates for euvolemia through goal-directed fluid therapy optimizing stroke volume through the perioperative period with the resulting effect of optimizing splanchnic and tissue perfusion while avoiding hypervolemia and fluid excess.

Surgical Site Infection Reduction Bundles

Surgical site infections occur at great economic cost to society—an estimated $3.5–10 billion in the United States alone—and are a major cause of both morbidity and mortality [147, 148]. The recognition that most infections are preventable has led to the implementation of many interventions to reduce surgical site infections after gynecologic surgery. The root causes of SSI include patient risk factors (e.g., obesity, hyperglycemia, immunosuppression), institutional factors (sterile processing, facilities), and suboptimal perioperative management. This section will focus on the last category, which is under comparatively greater control by the surgical team. However, it is worth emphasizing that no matter how perfect, no perioperative pathway will result in low infection rates in the face of flawed sterile processing, and it may be an important reason that SSI rates vary so greatly between institutions. Many elements and decision points in the perioperative workflow impact SSI; for these reasons, initiatives to lower SSI rates commonly include bundles of interventions (3–5 at minimum) rather than a single intervention alone. While this practice makes determination of the most important elements difficult, they have nevertheless been shown to be efficacious in reducing rates of SSI.

Three interventional studies have published results following implementation of SSI reduction bundles in patients undergoing surgery for gynecologic malignancies, with and without enteric resections. Baseline infection rates varied from 6% to 37%, demonstrating the huge variation across facilities due to case mix, patient mix, and institutional factors. All interventions were successful, reducing SSI to a range of 1.1–12% [64, 149, 150]. Of note, each bundle investigated varied slightly from one another but shared many common elements. These included standardized patient education with use of 4% chlorhexidine gluconate for daily showering; the use of preoperative and, when appropriate, intraoperative prophylactic antibiotic prophylaxis; preoperative and intraoperative skin preparation with 4% chlorhexidine gluconate; use of a sterile closing tray with re-gloving and re-gowning for fascia and skin closure of type II incisions; attention to perioperative glycemic control with a goal of <180 mg/dL; good hand hygiene by all providers in the care team; use of a sterile dressing for at least 24–48 hours after surgery; and early follow-up with the surgical team post-discharge. While the improvement in SSI rates referenced here included patients undergoing laparotomy, these principles should also be followed for patients undergoing minimally invasive surgery. The use of minimally invasive surgery is itself very effective in reducing SSI; in one investigation rates were 14-fold higher in patients undergoing laparotomy [151].

Patient-Reported Outcome (PRO) Measures

There are multiple dimensions to postoperative recovery, including physical, physiological, social, psychological, and economic factors [152]. Patient-reported outcome (PRO) instruments measure any aspect of a patient's health status with information derived directly from the patient [153]. As such, PRO instruments are uniquely able to measure the varied domains of recovery. To date, there is a paucity of PRO studies focusing on gynecologic patients within ERAS programs. One study that utilized the MD Anderson Symptom Inventory to measure longitudinal symptom burden demonstrated that patients on an ERAS pathway were found to have improvements in symptom burden and functional recovery compared to those not on an ERAS pathway [12].

Careful consideration of PRO instrument selection should include evaluation of the specific content and purpose of the instrument, responsivity in a surgical population, designed recall period, minimally important difference, and mode of administration. Timing of measures must include a preoperative baseline, with the remainder of measurements designed thoughtfully based on a priori hypothesis to balance patient burden with expected fluctuations in the PRO responses. A joint consensus statement by the American Society for Enhanced Recovery and Perioperative Quality Initiative on PROs in enhanced recovery pathways suggests

that institutions consistently document PROs within their enhanced recovery programs [154]. Specific recommendations included utilizing the quality of recovery score-15 (QoR-15) [155] for PRO assessment during the immediate postoperative period and the World Health Organization Disability Assessment Schedule (WHODAS) 2.0 [156] or Patient-Reported Outcomes Measurement Information System (PROMIS) measures for post-discharge assessments at 30 days and 90 days postoperatively [154, 157]. It is important to note that the QoR-15 was not developed or validated in a large proportion of gynecologic patients. Further research is encouraged to validate existing instruments or create new specific instruments to adequately capture symptom burden and recovery from the patient's viewpoint.

Minimally Invasive Surgery

With currently available data, it is not clear whether ERAS has a greater impact on minimally invasive surgery (MIS) or if MIS has a greater impact as one of the tenets of ERAS. Surgical trauma induces a well-documented physiologic stress response, which includes a cascade of hormonal and metabolic changes, as well as alterations in organ function [158]. One of the key tenets of ERAS from its inception was a focus on the reduction of complications by both decreasing the stress response and by modifying the metabolic response to surgical insult [1]. Laparoscopic surgery has been associated with a decrease in both the inflammatory and immunomodulatory response compared to open surgery [159, 160]. While some studies suggest that classic endocrine metabolic responses are less influenced by MIS, other studies have suggested that MIS decreases the cortisol stress response compared to moderate and highly invasive surgeries [161]. Given the published benefits of MIS in relation to the reduction in surgical stress, MIS was included as an element within the published ERAS practice guidelines for gynecologic surgeries. Specifically, the guidelines state that "MIS is recommended for appropriate patients when expertise and resources are available" [8]. There is a paucity of studies focusing on the impact of ERAS in MIS gynecologic surgery. In at least one retrospective series, ERAS implementation in MIS demonstrated an association with improvements in length of stay and cost [162]. Another series described an association of ERAS implementation with decreased intraoperative and postoperative morphine equivalents, decreased cost, and increased patient satisfaction [163]. Within the changing landscape of the application of MIS in gynecologic oncology, special attention should be paid to the word "appropriate" within the guideline statement. Recent evidence from a randomized trial suggests that in early cervical cancer, women undergoing MIS have higher recurrence rates and worse survival. Thus, benefits of MIS need to be carefully weighed against oncologic outcomes [164].

Conclusion

The ERAS gynecologic/oncology guidelines have helped integrate existing knowledge into practice and aligned perioperative care within our discipline. Future investigations using EIAS Gynecology will address knowledge gaps and improve clinical outcomes for patients.

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Enhanced Recovery After Surgery: Cesarean Delivery

47

R. Douglas Wilson, Jeffrey Huang, Cathy Cao, and Gregg Nelson

Introduction

Enhanced recovery after surgery (ERAS) programs are standardized, perioperative care pathways that—when combined with an audit (measure)/evaluation process for use (positive outcome) and against use (negative outcome) system with a dedicated multidisciplinary team—result in diminished surgical stress, enhanced patient physiologic and functional recovery, and decreased hospital length of stay (LOS) and complications [1–4].

There has been little implementation of ERAS in obstetrical surgery. A recent uncontrolled, observational study demonstrated that an enhanced recovery pathway could be successfully integrated into a labor and delivery unit. This program has resulted in a substantial increase in the number of patients leaving hospital 1 day after elective cesarean delivery (CD) compared to those leaving on the second postoperative day [4]. There was no difference in hospital readmissions among the two groups. The results suggested that an ERAS program could be successfully implemented into labor and delivery units [4].

In 2014, the Canadian Institute for Health Information (CIHI) and healthydebate.ca reported that cesarean delivery rates had increased from 17% of all births in 1995 to 29% in 2010/2011 [5]. The repeat CD rate for this group (would allow for scheduled CD innovation) was 76–90% and accounted for 11.3% of all deliveries in five Canadian provinces for the period of 2007–2011 [6].

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When Do You Start the ERAS Cesarean Delivery Process?

There is much debate about when to start the ERAS cesarean delivery (ERAS CD) process. The "focus" is directly on the surgical cesarean delivery process rather than the larger "optimized" vision of woman, pregnancy, and outcome for mother and baby.

The proposed "focused and optimized" process/elements of ERAS relevant to surgery and the cesarean delivery are summarized in Fig. 47.1.

There are certain modifiable and non-modifiable obstetrical confounders that increase the "probable" use of CD for delivery such as maternal body mass index (BMI) > 40 and other maternal comorbidities (Table 47.1, Fig. 47.2).

Each ERAS CD element (focused/optimized) has recommendation(s) with evidence level/recommendation grade. Table 47.2 summarizes the ERAS CD recommendations (see Chap. 46 for the GRADE working group level of evidence and strength definitions).

Optimized Preconception and Antenatal Care Period

Patient and Family Education

During preconception and antenatal maternity education, healthcare providers should provide preconception and pregnant women evidence-based education information and support. This evidence-based information about possible or planned cesarean delivery can help pregnant women recognize their obstetrical care requirements and also help women with informed decision-making [7].

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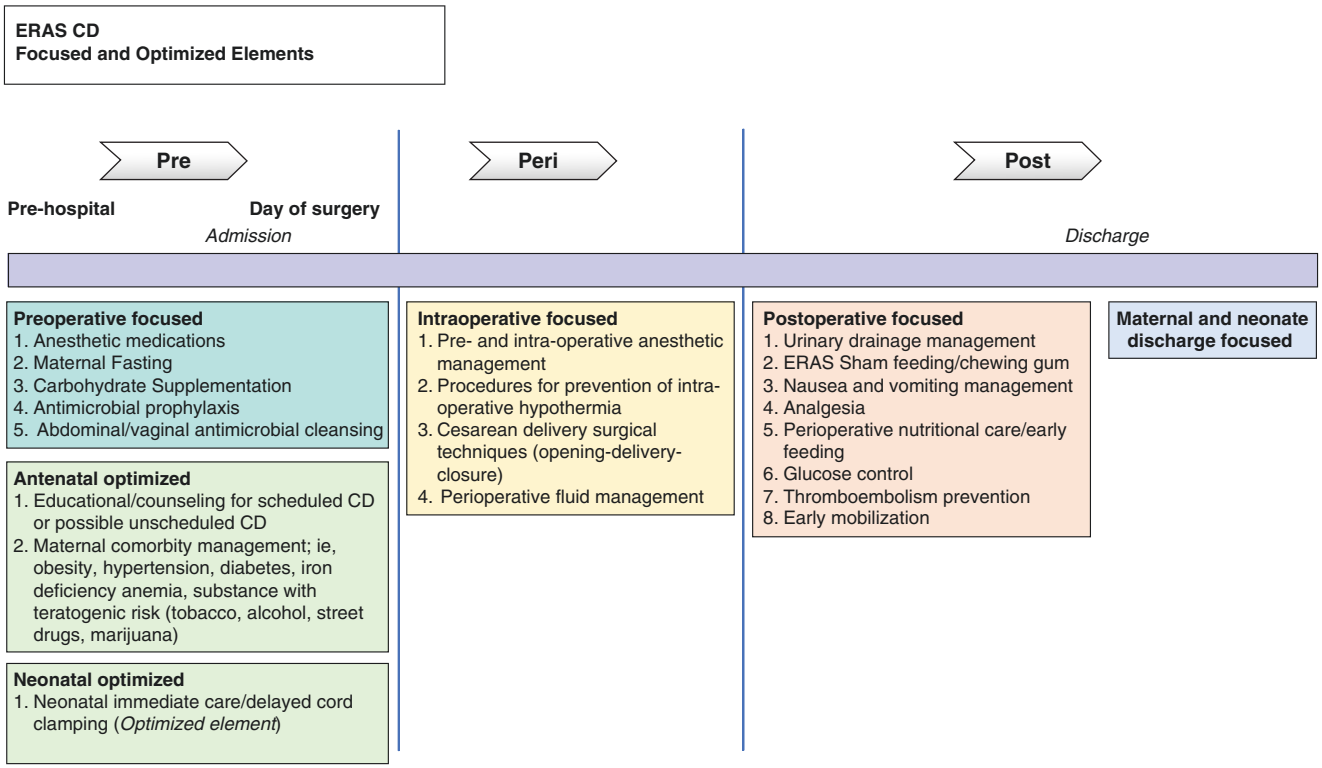

Fig. 47.1 ERAS cesarean delivery (CD) focused and optimized elements [36–38]

Table 47.1 ERAS for cesarean delivery: preoperative modifiable clinical factors

Non-modifiable clinical factor	Modifiable clinical factors/audit
Maternal age	
Paternal age	
Past history (obstetrics/medical/surgery/BMI)	Optimization of selected comorbidities (hypertension/diabetes/anemia/smoking) (SGA/LGA/SB/PTB < 34 weeks)
Family history (genetics/birth defects/multifactorial disease)	Surgical pathway (preoperative, intraoperative, postoperative)
Gestational weeks 0–20 (chromosomes/birth defects/miscarriage)	

BMI body mass index, *SGA* small for gestational age, *LGA* large for gestational age, *SB* stillborn, *PTB* preterm birth

Antenatal Care Optimization

Antenatal medical optimization is necessary to decrease the associated risk with surgery. Preconception and pregnant women with poor nutrition status, obesity, hypertension, diabetes, iron deficiency anemia, and substance use (tobacco, marijuana, alcohol) should be routinely assessed and counseled prepregnancy or during the first trimester [8–20].

Focused Preoperative Period: 30–60 Minutes

Scheduled or Unscheduled Cesarean Delivery

Anesthetic Medications

Antacids and histamine H2 receptor antagonists should be administered as premedication to reduce the risk from aspiration pneumonitis [21]. Preoperative sedation should not be used for scheduled cesarean delivery because of the potential for detrimental effects on the mother and neonate [22].

A meta-analysis including a Cochrane review of 22 randomized controlled trials (RCTs) showed that intake of clear fluids until 2 hours before surgery did not increase gastric content, reduce the pH of the gastric fluid, or increase complication rates compared with fasting overnight [23]. The American Society of Anesthesiologists (ASA) recommends that pregnant women undergoing elective surgery should have a fasting period for solids of 6–8 hours depending on the type of food ingested; they may have clear liquids up to 2 hours before induction of anesthesia [24]. Before surgical procedures, consider the timely administration of non-particulate antacids, histamine H2 receptor antagonists, and/or metoclopramide for aspiration prophylaxis [24].

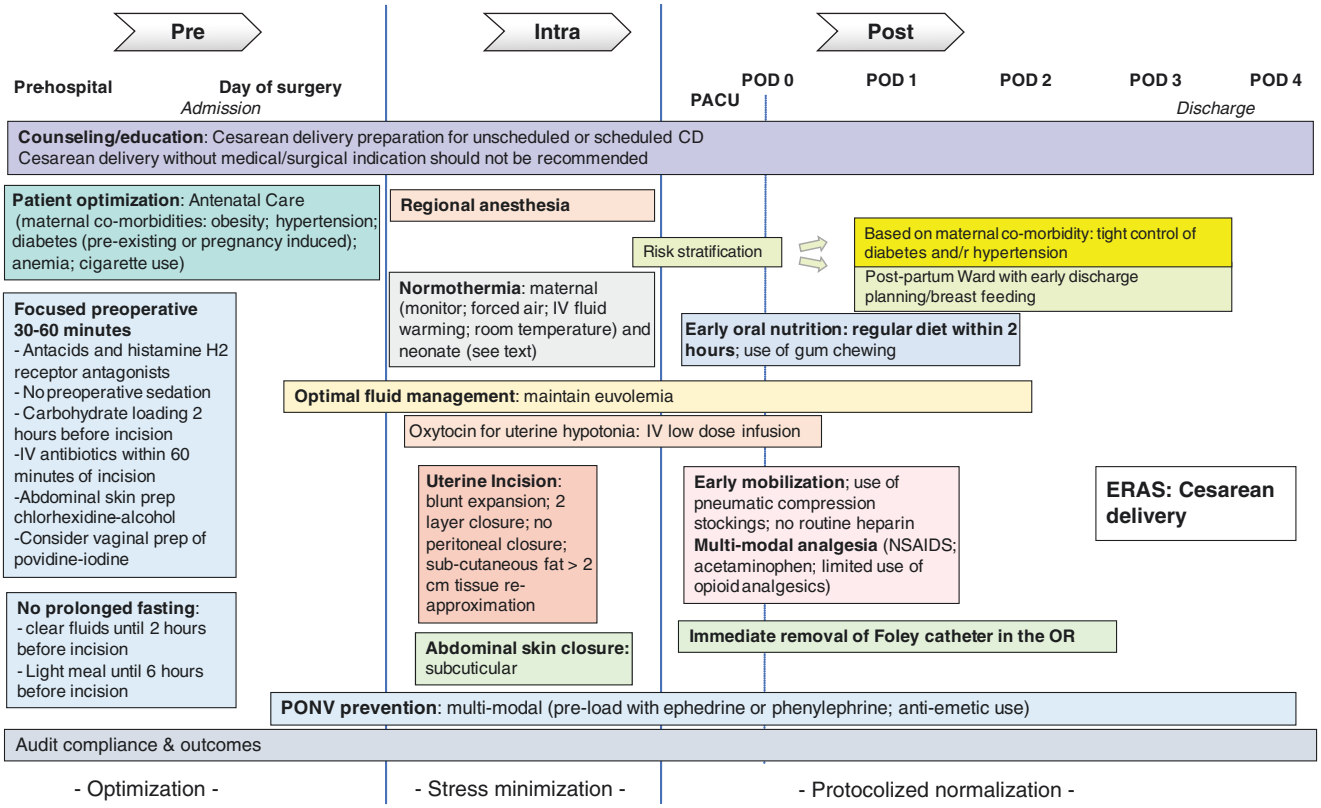

Fig. 47.2 ERAS treatment pathway for cesarean delivery (CD). *PACU* postanesthesia care unit, *IV* intravenous, *PONV* postoperative nausea and vomiting, *NSAIDs* nonsteroidal anti-inflammatory drugs, *OR* operating room

Table 47.2 ERAS cesarean delivery (CD) recommendations: focused and optimized protocols

ERAS CD recommendations	Evidence level	Recommendation strength
"Focused" preoperative recommendations		
1. Although high-quality evidence is lacking, good clinical practice would include informing the patient about procedures before, during, and after the cesarean delivery. The information should be adapted to whether the cesarean delivery is an unscheduled or is a scheduled surgery	Very low to low	Strong
2. Cesarean delivery without medical indication should not be recommended without a solid preadmission evaluation of the harms and benefits, for both mother and her baby	Very low to low	Strong
3. Antacids and histamine H2 receptor antagonists should be administered as premedication to reduce the risk from aspiration pneumonitis	Low	Strong
4. Preoperative sedation should not be used for a scheduled cesarean delivery because of the potential for detrimental effects on the mother and neonate	Low	Strong
5. Women should be encouraged to drink clear fluids (pulp-free juice, coffee, or tea without milk) until 2 hours before surgery	High	Strong
6. A light meal may be eaten up to 6 hours before surgery	High	Strong
7. Oral carbohydrate fluid supplementation, 2 hours before a cesarean delivery, may be offered to nondiabetic women	Low	Weak
8. Intravenous antibiotics should be administered routinely within 60 minutes before the cesarean delivery skin incision. In all women, a first-generation cephalosporin is recommended; in women in labor or with ruptured membranes, the addition of azithromycin confers additional reduction in postoperative infections	High	Strong
9. Chlorhexidine-alcohol is preferred to aqueous povidone-iodine solution for abdominal skin cleansing before cesarean delivery	Low	Strong
10. Vaginal preparation with povidone-iodine solution should be considered for the reduction of post-cesarean infections	Moderate	Weak

(continued)

Table 47.2 (continued)

ERAS CD recommendations	Evidence level	Recommendation strength
"Focused" intraoperative recommendations		
1. Regional anesthesia is the preferred method of anesthesia for cesarean delivery as part of an enhanced recovery protocol	Low	Strong
2. Appropriate patient monitoring is needed to apply warming devices and avoid hypothermia	Low	Strong
3. Forced-air warming, intravenous fluid warming, and increasing operating room temperature are all recommended to prevent hypothermia during a cesarean delivery	High	Strong
4. Blunt expansion of a transverse uterine hysterotomy at time of cesarean delivery is recommended to reduce surgical blood loss	Moderate	Weak
5. Closure of the hysterotomy in two layers may be associated with a lower rate of uterine rupture	Low	Weak
6. The peritoneum does not need to be closed because closure is not associated with improved outcomes and increases operative times	Low	Weak
7. In women with ≥2 cm of subcutaneous tissue, re-approximation of that tissue layer should be performed	Moderate	Weak
8. The skin should be closed with a subcuticular suture in most cases, because of the evidence of reduced wound separation compared to those women with staples and removal <4 days postoperatively	Moderate	Weak
9. Perioperative and intraoperative euvolemia are important factors in patient perioperative care and appear to lead to improved maternal and neonatal outcomes after cesarean delivery	Low moderate	Strong
"Focused" postoperative recommendations		
1. Urinary catheter should be removed immediately after cesarean delivery, if placed during surgery	Low	Strong
2. Fluid preloading, the IV administration of ephedrine or phenylephrine, and lower limb compression are effective to reduce hypotension and the incidence of intraoperative and postoperative nausea and vomiting	Moderate (multiple interventions)	Strong
3. Antiemetic agents are effective to prevent PONV during cesarean delivery. Multimodal approach should be applied to treat PONV	Moderate	Strong
4. Pneumatic compression stockings should be used to prevent thromboembolic disease in patients undergoing cesarean delivery	Low	Strong
5. Heparin should not be routinely used for VTE prophylaxis in post-cesarean patients	Low	Weak
6. Multimodal analgesia including regular NSAIDs and paracetamol is recommended for enhanced recovery for cesarean delivery	Moderate	Strong
7. A regular diet within the 2 hours after cesarean delivery is recommended	High	Strong
8. Gum chewing appears to be effective and is low-risk. It may be a redundant treatment if a policy for early oral intake is being used. However, it should be considered if delayed oral intake is planned	Low	Weak
9. Tight control of capillary blood glucose is recommended	Low	Strong
10. Early mobilization after cesarean delivery is recommended	Very low	Weak
11. Standardized written discharge instructions should be used to facilitate discharge counseling	Low	Weak
"Optimized" recommendations		
Antenatal		
1. Maternal obesity (body mass index >40 kg/m2) significantly increases the risks of maternal and fetal complications. Optimal gestational weight gain management should be used to control their weight during pregnancy. Surgical complexity requires multidisciplinary planning	High	Strong
2. Maternal hypertension should be managed during the pregnancy because maternal chronic hypertension has been found to increase significantly the incidence of maternal and fetal morbidity and cesarean delivery	High	Strong
3. Maternal gestational diabetes mellitus has been found to significantly increase the risk for maternal and fetal morbidity. Maternal diabetes should receive timely and effective management during preconception and pregnancy	High	Strong
4. Maternal anemia during pregnancy is associated with low birthweight and preterm birth and increases perioperative morbidity and mortality rates. The cause of the anemia should be identified and corrected	Moderate	Strong

ERAS CD recommendations	Evidence level	Recommendation strength
5. Maternal cigarette smoking is associated with adverse medical and reproductive morbidity and should be stopped before or in early pregnancy	High	Strong
Immediate neonatal care		
1. Delayed cord clamping for at least 1 minute at a term delivery is recommended	Moderate	Strong
2. Delayed cord clamping for at least 30 seconds at a preterm delivery is recommended	Low moderate	Strong
3. Body temperature should be measured and maintained between 36.5 °C and 37.5 °C after birth through admission and stabilization	Low moderate	Strong
4. Routine suctioning of the airway or gastric aspiration should be avoided and used only for symptoms of an obstructive airway (by secretions or meconium)	Low	Strong
5. Routine neonatal supplementation with room air is recommended because the use of inspired air with oxygen may be associated with harm	Low moderate	Strong
6. In all settings that perform cesarean delivery, a capacity for immediate neonatal resuscitation is mandatory	High	Strong

IV intravenous, *PONV* postoperative nausea and vomiting, *VTE* venous thromboembolism, *NSAIDs* nonsteroidal anti-inflammatory drugs

One RCT showed carbohydrate loading before surgery accelerated recovery, reduced postoperative insulin resistance and associated increased risks for complications, and reduced hospital length of stay (LOS) [25]. There is no study that has assessed the effect of carbohydrate drinks before elective CSD.

An RCT evaluation of preoperative oral carbohydrate use reported improved breastfeeding after CD for time to first breastfeeding and breastfeeding frequency and duration [26].

Antimicrobial Prophylaxis and Vaginal/Abdominal Skin Preparation

CD antibiotic prophylaxis that is administered preoperatively has significantly reduced the incidence of maternal infection especially endometritis and wound infection compared with administration of antibiotics after neonatal umbilical cord clamping [27–29]. An RCT showed that the addition of 500 mg of intravenous azithromycin to standard regimens for antibiotic prophylaxis before cesarean delivery further reduced the rate of endometritis, wound infection, and serious maternal adverse events [29].

An RCT showed the use of chlorhexidine-alcohol for preoperative skin antisepsis resulted in a significantly lower risk of surgical site infection (SSI) after cesarean delivery than did the use of iodine-alcohol [30].

Focused Intraoperative Cesarean Delivery

Obstetrical Anesthesia Choice

The advantages of regional over general anesthesia for cesarean delivery are well established. A prospective study showed that spinal anesthesia for elective cesarean delivery is associated with a shorter length of postoperative hospital stay [31]. Regional anesthesia enables early oral intake and recovery of gastrointestinal (GI) functions with lower oxytocin consumption, prolonged interval to first analgesic requirement [31].

Maternal and Neonate Hypothermia Prevention

Perioperative hypothermia is estimated to occur in more than 60% of patients undergoing cesarean delivery [32]. Perioperative hypothermia is associated with surgical site infection, myocardial ischemia, an altered drug metabolism, coagulopathy, prolonged duration of hospitalization, shivering, reduced skin integrity, and poor patient satisfaction [33, 34].

An RCT showed a warmed intravenous (IV) fluid load and a lower body forced-air warming blanket for scheduled cesarean delivery under spinal anesthesia increased maternal temperature on arrival at the postanesthesia care unit (PACU), minimized the perioperative temperature drop, decreased the incidence of perioperative hypothermia, and improved maternal thermal comfort [35].

Surgical Techniques and Abdominal Entry

ERAS is a systematic quality improvement process that has published three guidelines with elements in focused (30–60 minutes pre-skin incision to maternal/neonate hospital discharge) and optimized (antenatal, maternal comorbidity management) pathways for cesarean delivery pre-, intra-, and postoperative periods including immediate neonatal care at delivery [36–38]. Table 47.3 summarizes the more detailed ERAS abdominal entry, hysterotomy entry, and abdominal closure technique with their evidence and recommendation grading [37, 39–41].

Table 47.3 ERAS abdominal entry and hysterotomy entry and closure technique [37, 39–41]

Intraoperative	ERAS element/process	Recommendation for	Recommendation against	Reference
Abdominal entry	Skin incision type	Moderate weak		[40, 41]
	Pfannenstiel	Moderate strong		[39]
	Joel-Cohen	Moderate strong		[39]
	Second scalpel		Moderate strong	[40]
			weak	[39]
	Rectus muscle cutting		Moderate strong	[40]
Hysterotomy	Uterine incision: transverse	Moderate weak		[38]
	Blunt expansion: cephalad-caudad	Moderate weak		[37(ERAS CD)]
		High strong		[39, 40]
	Closure: two layer	Low weak		[37(ERAS CD)]
		Moderate weak		[39, 40]
	Continuous suture	Moderate weak		[40]
Abdominal closure	Bladder flap		Moderate strong	[40]
	Peritoneum left open	Low weak		[37(ERAS CD)]
		Moderate strong/weak		[39, 40]
	Rectus muscle		Low weak	[40]
	Fascia	Moderate strong		[39]
	Subcutaneous	Moderate weak		[37(ERAS CD)]
	^2 cm depth	High strong		[39, 40]
	Wound irrigation		Low weak	[40]
	Skin closure	Moderate weak		[37(ERAS CD)]
	subcuticular	Moderate weak		[40]
	Oxytocin	Low weak		[39]

Maternal Fluid Management

Maintaining maternal euvolemia is the key to achieve optimal outcomes after surgery. Intravascular volume is one of the important factors of cardiac output and oxygen delivery. Optimal uterine perfusion is not only required for adequate fetal oxygenation but also for the delivery of nutrients and the elimination of waste products from the contracting myometrium [42]. Maternal fluid overload has also been associated with increased cardiovascular work and pulmonary edema [43]. There are additional concerns over newborn weight loss during the first 3 days following birth that occurs when mothers have received large volumes of intravenous fluids [44].

Therefore, adequate fluid therapy with vasopressors could be effective to reduce incidence and severity of hypotension during spinal anesthesia for cesarean section [45]. Minimally invasive hemodynamic monitors have been used to detect flow-related parameters of fluid responsiveness to optimize end-organ tissue perfusion (goal-directed intravenous fluid therapy [GDFT]) [46, 47]. However, there was little published data about the effects of GDFT during CD. High-quality research trials need to be conducted to clarify this recommendation.

Prevention of Uterine Hypotonia: Oxytocin Dose

Administration of oxytocin after the newborn is delivered reduces postpartum blood loss and risk of hemorrhage. However, the optimal dose and route of administration (i.e., bolus dose versus infusion of oxytocin at CD) are debatable [48]. Since the elective cesarean delivery has minimal concern of prior prolonged exposure to oxytocin and related desensitization, it is not necessary to apply bolus, which might cause hypotension, nausea and vomiting, or even electrocardiogram changes.

Foley Catheter Removal

Traditional indications for indwelling Foley catheter included the need for measured urine output (e.g., hemorrhage, hypertension), urinary tract injury, and/or postoperative urinary retention/failed voiding efforts.

A prospective clinical trial has demonstrated that the mean postoperative ambulation time, time till the first voiding, and length of hospital stay were significantly shorter in women who had immediate removal of the catheter compared with women who had the catheter removed after 12 hours [49].

Neonatal Immediate Care in the Operating Room

This optimized ERAS CD element is important as these surgical processes have impact on both maternal and neonatal outcomes. This resuscitation process is usually away from

the maternal surgical field, but close communication with the mother is required. Pediatric/neonatology medical and nursing team members are generally in attendance, but this is dependent on location and standard hospital policies [37].

Focused Postoperative Cesarean Delivery

Maternal Prevention of Postoperative Nausea and Vomiting

Nausea and vomiting are common symptoms experienced during cesarean delivery under regional anesthesia and may occur in the postoperative period following cesarean section under either regional or general anesthesia [50]. There are multiple underlying causes of nausea and vomiting at cesarean delivery. Postoperative nausea and vomiting (PONV) reduced patient dissatisfaction and delayed discharge from hospital. There are no prospective observational studies to estimate the exact incidence of nausea and vomiting during cesarean delivery and in the postoperative period. The identified risk factors are hypotension, reduced cardiac output from aorto-caval compression, surgical stimulation, and intraoperative medications such as opiates and uterotonics including Pitocin and particularly ergometrine [51].

A multimodal approach to PONV prevention is becoming an expectation for the standard of care. These interventions include 5-hydroxytryptamine receptor (serotonin) (5-HT3) antagonists, dopamine antagonists, and sedatives [51].

Prophylaxis Against Maternal Thromboembolism

Venous thromboembolism (VTE) is associated with considerable maternal morbidity and mortality. Pregnancy is associated with a number of physiological and anatomic changes that increase the risk of VTE and include a hypercoagulable state, increased venous stasis, decreased venous outflow, compression of the inferior vena cava and pelvic veins by the enlarging uterus, and decreased mobility [52]. Other pregnancy-related factors identified to increase the risk include multiple gestations, preeclampsia, prolonged labor, and cesarean delivery [53].

Pharmacological agents—such as heparin, Lovenox, and aspirin—have been used in VTE prevention due to their anticoagulant properties, but caution is required when used with neuraxial block [54]. Non-pharmacological methods—such as graduated compression stockings, intermittent pneumatic compression, or venous foot pumps—have been used for their ability to reduce venous stasis and blood stagnation by promoting venous blood flow through external compression [54].

Postoperative Analgesia (Multimodal Analgesia)

The goal of multimodal analgesia is to minimize the use of and side effects from opioids and to speed up the overall postoperative recovery quality [55]. The disruptive physiological and psychological consequences from poorly managed pain can lead to delayed recovery and postpartum frustration and depression, as well as contribute to the emotional detachment of the mother from her newborn [56].

Split doses of oral opioid use in a post CD order set was associated with a 56% reduction in the 48-hour opioid use [57]. Review and management of non-opioid pain management requires directed medication use [58, 59].

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory agents (NSAIDs) are potent analgesics that function as inhibitors of cyclooxygenase and prostaglandin synthesis. Ideally, NSAIDs should be administered as the first option for breakthrough pain after giving neuraxial long-acting opioids. If CD is done without neuraxial anesthesia, then either IV and/or PO NSAIDs should be used as the scheduled "around the clock" first-line analgesics instead of IV opioids. Recent meta-analysis demonstrated that the perioperative use of IV/intramuscular (IM) NSAIDs in CD patients resulted in significantly lower pain scores, less opioid consumption, and less drowsiness/sedation but no difference in nausea or vomiting compared to those who did not receive NSAIDs [60].

Even though there is theoretical concern that NSAIDs are associated with platelet dysfunction, gastrointestinal irritation/bleeding, and renal dysfunction, clinically it is safe to administer ketorolac in postpartum patients. A recent meta-analysis reveals that IV ketorolac does not increase bleeding [61].

Acetaminophen

As with NSAIDs, IV or PO acetaminophen should be administered on a "scheduled basis" to achieve the optimal effect. Acetaminophen and NSAIDs together will bring an additive if not synergistic analgesic result [62]. One caveat is its potential liver toxicity—the maximum dosage for obstetric patients should be limited to 3–4 g/day (i.e., 60 mg/kg/day).

Opioid Analgesics

Traditionally, IV PCA (patient-controlled analgesia) has been prescribed as the gold standard regimen for post CD patients when neuraxial techniques have not been used or

have failed. Continuous background infusion is not recommended in an opioid-naïve parturient, as there may be a higher risk for respiratory depression [63]. However, given the multiple side effects related to the opioids such as nausea, vomiting, decreased gastrointestinal movement, pruritus, urinary retention, sedation, and respiratory depression, opioids have become the least favorable regimen in the era of enhanced recovery after surgery [63].

Other Adjuvant Agents

- Gabapentinoids [64]
- Tramadol [63]
- N-methyl-D-aspartate (NMDA) antagonists: ketamine [65]
- Alpha-2-agonists [66]
- Glucocorticoids [67]

Oral Nutrition

Upon arrival in the post anesthesia care unit after CD, as soon as patients are fully awake, they should be encouraged to drink. If they can tolerate some oral fluids, they can be advanced to eat a normal diet. The presence of fluid and semi-digested food in the gut elicits all natural gut-stimulating reflexes via sight, smell, taste, salivation, mastication, and swallowing. The replenishment of good and balanced nutrition will help generate healthy milk to feed the baby. Early oral intake after CD is safe, enhances bowel function recovery, and does not increase the incidence of postoperative ileus [68]. Following blood glucose levels and treating abnormal values in diabetics are also important to prevent gastroparesis. A meta-analysis (81 studies and 9000 participants) showed that patients who chewed gum after an operation have bowel movements sooner and have shorter hospital stays than people who did not chew gum [69]. Chewing gum may not have been able to show clear benefit in all trials, but it is a cheap and easy intervention with unknown adverse effect.

Prevention of Postoperative Ileus

Given the exact etiology of postoperative ileus (POI) is unclear and has multifactorial aspects, there needs to be consideration of the many complex interactions when successful ERAS pathway is implemented to combat POI, including autonomic dysfunction to stress response, activation of gut opioid receptors, GI hormone imbalance with gut peptides alteration, electrolyte derangement, impaired GI contractility and intestinal wall stretch with edema, as well as activation of mast cells, monocytes, and macrophages, releasing histamine and cytokines [70].

Even though current research data have not shown definitive evidence that an ERAS strategy will lead to diminished incidence of POI, the indirect evidence of decreased length of hospital stay and presumed alleviation of ileus-inducing stress factors support the implementation of enhanced recovery principles toward decreasing POI incidence [71].

Perioperative Glucose Control

Diabetes in pregnancy is associated with adverse outcomes, including an increase in morbidity and mortality for both mother and fetus [72, 73]. Patients with diabetes who undergo surgery have increased complications with wound infection, length of hospital stay, and death [74].

The level of control of capillary blood glucose (CBG) is a complex area, and lower limits of 4–8 mmol/L are recommended at the time of delivery to reduce fetal hypoglycemia [75]. The use of variable rate insulin infusions (VRII), previously known as a "sliding scale," is recommended—usually with endocrinology expertise. Type 1 diabetes patients receiving insulin should never stop their insulin as ketoacidosis may develop rapidly. The manipulation of perioperative insulin is complex, with small evidence base for patients undergoing cesarean delivery [76].

Oral carbohydrate preloading is an area of controversy for patients with impaired glucose control as in the nondiabetic surgery population it has shown value for reduced complication and length of stay [38].

Following delivery of the fetal/placental unit, maternal insulin requirements fall rapidly, and CBG should be checked if the patient is receiving insulin; diabetic expertise for both mother and baby management is required [77].

Early Mobilization and Rehabilitation

Preoperative physical movement and breathing exercises are correlated with enhanced ambulation and improved patient outcomes postoperatively. Postoperative pain and fatigue contributes to decreased mobility, which in turn results in suppressed cardiopulmonary and musculoskeletal system function. Early movement after CD will minimize the suppression and deconditioning; facilitate high-quality interaction between mothers and newborns; speed up returning to baseline function; and achieve the goal of better overall physical, mental, and economical outcomes [78, 79].

Early mobility helps patients maintain flexibility, strength, and endurance. Randomized controlled trials of enhanced recovery pathways (ERPs) have shown a decrease in atelectasis, pneumonia, thromboembolism, and delirium; increased muscle strength and tissue oxygenation; decreased opioid use; prevention of pressure ulcers; and potential benefit of

prevention of ileus; all of the ERPs include early ambulation. The timing of mobilization is crucial. The authors recommend a minimal 15 minutes on the day of CD and 3 hours on postoperative day 1, i.e., six times of 30 minutes, of walking. Ultimately, patient postoperative mobility and post-discharge rehabilitation should be adapted to meet the needs of each individual patient [38].

It is critically important to ensure the safety of both the mothers and the newborns after discharging home. An RCT of women discharged on day 1 or 2 following elective CD looked at two primary outcomes: patient satisfaction score and exclusive breastfeeding rates at 6 weeks. They found no difference between the two groups on either outcome [79].

Two issues need to be addressed before sending patients home earlier. One concern is the optimal timing of neonatal comprehensive examination. Most experts consider the neonatal exam should be performed ideally within 24 hours following CD [80]. Another caveat is that the provision of safe and robust follow-up community care after discharge will offset some of the cost savings from less in-hospital care [81].

In enhanced recovery, goals of discharge care are clearly communicated to the patient and family. Discharge instructions should include but not be limited to nutritional recommendations; medication changes; pain control; blood pressure and glucose monitoring and control; follow-up information with obstetrician, pediatrician, and primary care physician; and exercise recommendations.

Conclusion

ERAS elements have the potential to be successfully implemented in CD based on the evidence obtained from this review. The ERAS CD knowledge transfer and implementation will require multidisciplinary team coordination in the preoperative, intraoperative, and postoperative phases and the development of a formalized ERAS® CD guideline. Such a guideline will require pairing with an audit system (e.g., ERAS® Interactive Audit System) to enable teams to review their protocol compliance on a regular basis. The ERAS team (typically comprised of at least a surgeon, anesthesiologist, and nurse) determines where their compliance is low and then is able to focus their efforts on improving compliance, which then translates into improved clinical outcomes.

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ERAS in Spine Surgery

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Introduction

Spine surgery is one of the most recent specialties to adopt enhanced recovery after surgery (ERAS) principles. The success of ERAS programs in other specialties catalyzed this movement in order to approach several mounting challenges in spine surgery. Importantly, growing surgical demand, rising costs, and wide variability in hospital length of stay (LOS) outcomes across the globe favored the need for innovation, with enhanced recovery programs identified as a promising solution [1]. In addition to the broader benefits of ERAS programs such as reduced costs and faster recovery, spine surgery reaps benefits from standardized pain reduction interventions inherent to ERAS as well. Spine surgery, and in particular lumbar fusion, is regarded as one of the most painful surgical procedures [2]. This, in turn, predisposes to a risk for increased narcotics consumption and misuse among spine surgery patients. However, through commonly employed interventions in ERAS programs, the opioid crisis—which has hit the United States (US) particularly hard [3]—may be curbed.

Although numerous opportunities for improvements through ERAS implementation in spine surgery have been identified, at present, there are no published guidelines. Thus, assessment of a complete set of enhanced recovery elements in the field is yet to be elucidated, and literature examining such concepts remains limited. The aim of this chapter is to assemble the literature that could serve as the foundation for future development and testing of enhanced recovery programs in spine surgery and drive discussion at the international level for continual improvements in principles, techniques, and implementation strategies.

This chapter will explore the knowledge in various enhanced recovery topics within spine surgery. Additionally, the chapter will highlight studies that have already tailored certain enhanced recovery principles to this subspecialty. Finally, this chapter will identify important topics for future discussion of ERAS to shape its use in spine surgery.

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Recommendations for Spine Surgery

The current ERAS review for lumbar spinal fusion was developed based on specific search criteria, to allow a comprehensive review of the literature according to PRISMA guidelines to identify all relevant articles pertaining to the selected enhanced recovery topics and lumbar fusion surgery. Articles were narrowed down using strict inclusion and exclusion criteria and then underwent full-text review as the final part in the selection process. The following sections outline the current knowledge related to ERAS and its elements for lumbar fusion.

Preoperative Period

The first crucial intervention in every ERAS specialty guideline is patient education regarding the enhanced recovery process. Within lumbar surgery, the common perception of uncertain outcomes and lengthy recovery can be particularly challenging [4], but preoperative education programs have demonstrated improvements in patient satisfaction and decreased healthcare costs [5, 6]. The use of cognitive behavioral therapy and expectation setting for recommended psychological optimization overlaps with these interventions and may provide a greater benefit [7, 8]. In addition to managing patient expectations prior to surgery, optimizing the patient's health status through weight loss, if necessary, and prehabilitation programs is also recommended. Although no specific weight loss programs have been identified as superior, studies comparing prehabilitation exercise interventions under the guidance of physiotherapists to standard care demonstrated reductions in length of stay and improvements in satisfaction

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and outcome metrics such as the Oswestry Disability Index (ODI) or visual analogue scale (VAS) for back pain [9, 10]. As part of the health optimization goals for patients undergoing spine surgery, nutrition protocols designed to balance enteral supplementation and maintain euglycemia are recommended to prevent malnutrition and reduce complications [11, 12]. The deleterious effects of smoking, both biochemically and clinically, are well-described in the spine literature and include significantly increased risks of pseudoarthrosis, infection, and adjacent-segment disease [13]. To reduce complications and further optimize patient health, smoking cessation should be encouraged at least 4 weeks prior to surgery and maintained postoperatively [14].

Furthermore, two common elements integral to ERAS pathways were found to be effective interventions within lumbar fusion: multimodal analgesia preoperatively and fluid management perioperatively. Non-narcotic medication regimens that include pregabalin [15], nonsteroidal anti-inflammatory drugs (NSAIDs) [16], and ketamine [17] demonstrated the greatest pain management benefits for patients. A single study examined the use of a preemptive analgesic protocol that included celecoxib, pregabalin, extended-release oxycodone, and acetaminophen, which amounted to significant reductions in narcotic consumption postoperatively [18]. Additionally, goal-directed fluid therapy is commonplace in complex general surgery guidelines, but there is a paucity of literature on the subject related to spine surgery. One study showed a benefit for fluid management in spine surgery on five or more levels [19], but other studies did not demonstrate a benefit for surgeries of fewer levels [20, 21].

Intraoperative Period

Recommendations during the intraoperative period focus on three distinct surgical interventions. First, studies on antimicrobial prophylaxis have shown mixed results. The use of intravenous antibiotics prior to skin incision may lead to additional costs without much added benefit [22]. Application of intraoperative vancomycin powder, although common practice, does not appear to reliably reduce surgical site infections in spine surgery [23, 24]. Similarly, use of tranexamic acid [25] and cell saver devices [26] to control intraoperative blood loss has not demonstrated cost-effectiveness nor reduced blood losses in lumbar fusions less than three levels, and therefore usage is not recommended for these procedures.

One recommended intervention related to the overall multimodal analgesic approach is the intraoperative use of local injectable pain reduction techniques, which includes local, regional, and spinal anesthesia. Epidural administration of various analgesics is commonly employed, and many studies have shown a clear benefit in reducing pain scores and narcotics consumption [27, 28]. Field blocks with a combination of bupivacaine and clonidine have also augmented pain relief and may be used as well [29]. Most recently, studies examining liposomal bupivacaine, a long-acting local anesthetic, have shown reductions in both length of stay and acute care costs while also demonstrating decreased narcotics consumption compared to controls [30, 31].

Postoperative Period

There are a number of recommended interventions during the postoperative period, many of which are also similar to other specialty guidelines. Central to all ERAS recommendations are multimodal analgesic protocols, a few of which have already been discussed in this chapter for the preoperative and intraoperative periods. During the postoperative period, a similar medication protocol is recommended and includes a combination of non-narcotic medications such as acetaminophen, NSAIDs, gabapentin, S-ketamine, dexamethasone, ondansetron, and epidural local anesthetic infusion or patient-controlled analgesia with morphine [32]. Use of multimodal analgesic protocols that limit the amount of opioids consumed also helps to alleviate postoperative nausea and vomiting (PONV), which is common after surgery [32]. Although ramosetron appears to be a more efficacious antiemetic, it is not currently available in the United States, and, therefore, ondansetron remains the recommended medication of choice [33]. Furthermore, the use of total intravenous anesthesia for non-intubated patients has demonstrated a lower incidence of PONV and thus may be used to reduce symptoms further [34].

Placement of urinary catheters is another common practice during surgery because it allows for close monitoring of kidney function and urine output, as well as provides comfort to patients who are slow to ambulate after surgery. However, early removal of urinary catheters is recommended to decrease length of stay and limit complications such as infection [35]. Also, prophylaxis against venous thromboembolism is advised through a multimodal approach that includes low-molecular-weight heparin, mechanical compression devices, and early mobilization [36–38].

Early mobilization is another important aspect in the ERAS guidelines for spine surgery. Programs should consist of physical therapy-led standing exercises on the day of surgery, followed by assisted and then independent intensive physiotherapy on subsequent postoperative days [9, 39]. Such early mobilization strategies should be the foundation for a rehabilitation program after surgery that improves the functional outcomes of patients as they recover on an outpatient basis.

A summary of the literature recommendations for lumbar fusion is shown in Table 48.1. The above findings represent

Table 48.1 Summary of ERAS recommendations for lumbar spinal fusion

Preoperative	
Patient education	Preoperative patient education of the enhanced recovery process is recommended
Weight loss	Preoperative weight loss is recommended
Prehabilitation	Prehabilitation exercise programs are recommended
Psychological optimization	Preoperative psychological optimization through CBT and expectation setting is recommended
Nutritional optimization	Preoperative nutritional optimization through enteral supplementation, euglycemic maintenance, and smoking cessation is recommended
Non-narcotic medications	Use of multimodal analgesic regimens that include pregabalin, NSAIDs, and ketamine preoperatively is recommended
Perioperative fluid management	Goal-directed fluid therapy should be used for fusions at 5 or more levels but is not recommended for 1–2 level fusions
Intraoperative	
Antimicrobial prophylaxis	Intravenous antibiotic prophylaxis prior to skin incision is recommended
Local and injectable pain reduction techniques	Use of long-acting local anesthetics such as liposomal bupivacaine is recommended. Use of epidural analgesics or field blocks is also recommended
Blood loss protocol	Use of tranexamic acid, aminocaproic acid, or cell saver devices is not recommended
Postoperative	
Nausea and vomiting protocols	Use of ondansetron is recommended to control PONV. Use of multimodal analgesic protocols is also recommended to decrease opioid use and minimize PONV
Multimodal analgesia protocol	Use of multimodal analgesic regimens that include ketamine and acetaminophen is recommended. Use of NSAIDs following lumbar fusion is not recommended
Urinary catheter management	Early removal of urinary catheters is recommended
Thromboembolic prevention	Use of a multimodal prevention approach that includes low-molecular-weight heparin, mechanical compression devices, and rapid mobilization is recommended
Early ambulation	Intensive physiotherapy the day of surgery and each day during hospitalization is recommended
Rehabilitation	Participation in a structured physiotherapy program is recommended

Abbreviations: *PONV* postoperative nausea and vomiting, *CBT* cognitive behavioral therapy

the first review of enhanced recovery principles applied to spine surgery. These need to be further developed into a consensus protocol to allow studies examining the use of the complete set of recommendations. This will likely provide greater insight into the most effective strategies to optimally improve recovery, thus guiding future development of ERAS for this operation.

Current Implementation Strategies

A recent review of the spine literature found only a few published studies describing implementation of ERAS programs to a variety of different spine procedures [40]. One study from the United Kingdom discussed implementation of an elective spine surgery program in a hospital experienced in implementing enhanced recovery protocols for hip and knee arthroplasty [41]. The aim of the program was to institute interventions applicable to each of the elective spine procedures and to standardize enhanced care between surgeons, nurses, and physiotherapists. The program demonstrated a significant reduction in LOS from an average of 6 days down to 2.9 days and decreased readmission rates from 7% to 3%. Importantly, a median of 100% of patients stated their care was "good" or "excellent." Another study from the United Kingdom examined an enhanced recovery program for lumbar and cervical spine surgeries, finding that 95% of cases were classified as ambulatory and the remaining 5% as short-stay procedures [42]. The authors concluded that application of enhanced recovery principles to spine cases can be used to significantly shorten length of stay without increasing complications or readmissions. Preliminary results from an ERAS program in the United States for metastatic spine surgery have also demonstrated up to a 2-day decrease in LOS [43].

Two studies performed by the same institutional group developed an ERAS program for adolescent idiopathic scoliosis surgery [44, 45]. In addition to decreases in length of stay, both studies linked reductions in opioid usage and the effectiveness of early mobilization to the creation of a standardized multimodal analgesic regimen. Additionally, Gornitzky et al. included an analysis of ERAS protocol compliance, which provides additional evidence that high compliance rates lead to even better outcomes [44].

A Chinese team recently examined the use of ERAS for mobile microendoscopic discectomy-transforaminal lumbar interbody fusion (MMED-TLIF) [46]. The authors concluded that the addition of enhanced recovery elements to a minimally invasive TLIF procedure improved several outcome measures including intraoperative blood loss, postoperative pain scores, and LOS. Similarly, Wang et al.

previously demonstrated the success of enhanced recovery elements for improving outcomes and reducing acute care costs in one- and two-level endoscopic transforaminal lumbar interbody fusions [31, 47].

Building on the initial study, Wang et al. recently developed a novel "bottom-up" approach for staged implementation of three key elements of enhanced recovery at a time. Patients undergoing posterior, one-to-three level lumbar fusion with one of three spine surgeons received an intraoperative injection of liposomal bupivacaine, an intravenous infusion of 1 gram of acetaminophen immediately after surgery, and daily postoperative rounding checks by a member of the ERAS care team. A preliminary unpublished analysis after the first 3 months of implementation demonstrated that pain scores recorded by the physical/occupational therapy teams each day were consistently lower in the ERAS cohort compared to the control group, importantly on postoperative day (POD) 1 (4.35 vs. 6.52; Fig. 48.1). The total amount of oxycodone and meperidine consumed were also decreased in the ERAS group. Additionally, distance ambulated on each POD was increased in the ERAS cohort, with significance achieved on POD2 (186 ft. vs. 90.5 ft) and POD3 (290.4 ft. vs. 113.0 ft.; Fig. 48.2). LOS was decreased in the ERAS group (3.09 days) compared to the control cohort (3.72 days) but did not achieve significance.

The success of the studies and preliminary data described in this section indicates promise for the future of ERAS in spine surgery and highlights the importance of the upcoming guidelines. A standard set of recommendations for spine programs across the globe may enable more accurate monitoring of interventions that are providing the greatest benefit—and testing to elucidate which are not. Furthermore, collaboration among providers and programs regarding the most effective ways to boost protocol compliance will potentially alleviate some of the challenges to implementation that ERAS programs often face.

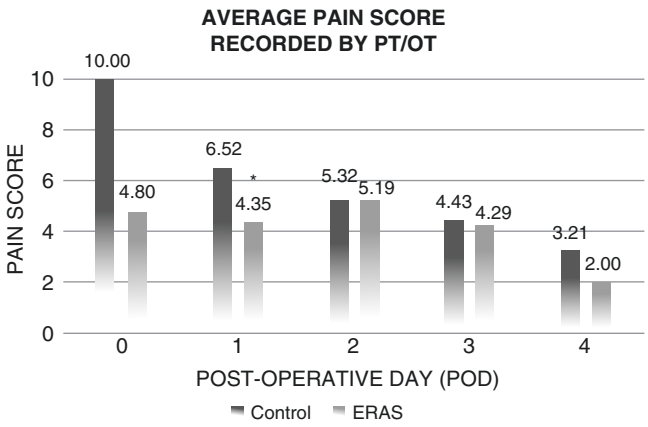

Fig. 48.1 Average pain score recorded by physical therapy/occupational therapy team on each postoperative day. ∗ denotes $p < 0.01$

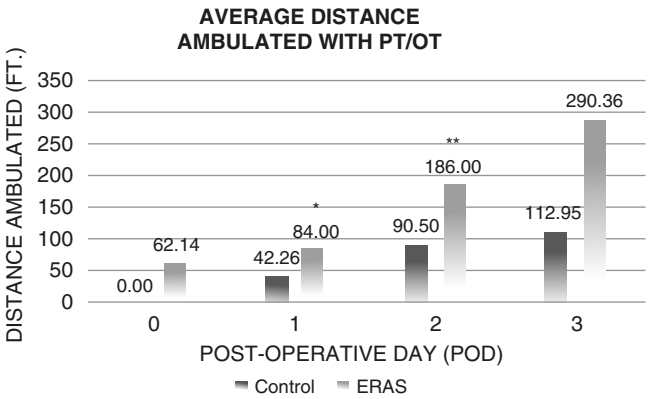

Fig. 48.2 Average distance ambulated with physical therapy/occupational therapy team on each postoperative day. ∗ denotes $p < 0.05$, ∗∗ denotes $p < 0.01$

Topics for Future Discussion

Because of the recent adoption of ERAS in spine surgery, discussion regarding the most effective interventions and implementation strategies has not yet evolved. While several groups around the world have begun applying enhanced recovery tenets to the field, each has incorporated general principles first outlined in other subspecialty guidelines (Fig. 48.3). Therefore, the publication of guidelines specific to spine surgery will likely foster a more focused discussion of interventions providing maximal benefit specifically to spine patients.

While developing the guidelines, there were several topics for which available literature pertaining to spine surgery was limited. For example, discussions of nutritional optimization and fluid management, while highly important for other fields, have not been rigorously examined in the spine literature as yet. Additionally, the literature regarding the most effective antimicrobial prophylaxis method does not permit a definitive recommendation, even though certain interventions are common practice. However, the use of various multimodal analgesic and antiemetic protocols has been widely studied for spine surgery in particular. Non-narcotic pain management is essential and universal for any ERAS program, but in spine, there has been a long debate as to the effects of NSAIDs on bony fusion following spine surgery. Therefore, further research will be needed to explore regimens providing the greatest benefit for patients enrolled in a comprehensive spine ERAS program. This will be the beginning of the iterative process inherent to other ERAS programs now applied to spine surgery for the first time.

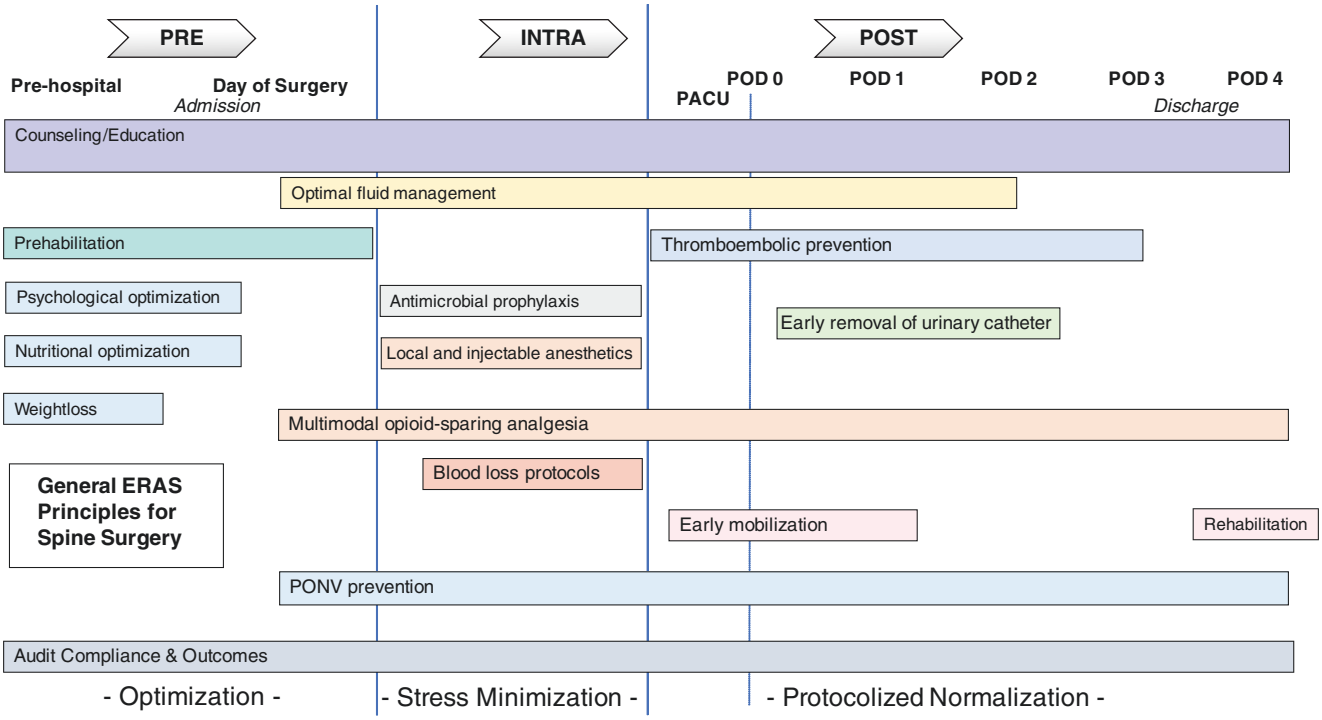

Fig. 48.3 General ERAS principles for spine surgery. PACU post-anesthesia care unit, PONV postoperative nausea and vomiting

Conclusion

Spine surgery is one of the most recent subspecialties to begin studying and incorporating ERAS into its practice. Enhanced recovery aims to minimize pain, speed recovery, and improve patient satisfaction through a multimodal approach and will help provide a greater benefit to patients undergoing spine surgery. Therefore, recommendations based on available evidence are being developed and will be published to guide spine programs. This initial iteration will serve as the foundation for future intervention and implementation strategies and foster discussion among providers in many disciplines to continually improve ERAS in spine. Several programs have already begun applying enhanced recovery principles to spine procedures, and the results have been promising. Thus, as demand for surgery increases and emphasis on healthcare value grows, ERAS should play an important role in the future of spine surgery.

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Orthopedic Surgery in Enhanced Recovery After Surgery

49

Thomas W. Wainwright and Tikki Immins

Background and History of ERAS in Orthopedic Surgery

The systematic implementation of an evidence-based perioperative care pathway—an enhanced recovery after surgery (ERAS) pathway (also known as fast-track)—has demonstrated that hospital length of stay and complications can be reduced, without increasing readmissions [1]. The first orthopedic surgeries to use ERAS pathways were total hip arthroplasty (THA) and total knee arthroplasty (TKA). These surgeries were chosen as they were both high volume, had long hospital length of stays, and carried high costs. ERAS pathways were first widely adopted in countries such as Denmark and the United Kingdom (UK) [2–5] through the use of centrally organized improvement programs. Their success led to their spread internationally, and their use is now broadly accepted as best practice for hip and knee arthroplasty surgeries (Fig. 49.1).

ERAS pathways aim to reduce a patient's recovery time following surgery and improve patient outcomes. To do this, orthopedic ERAS pathways encourage the patient to be active in the process of their recovery. Multidisciplinary teams focus on combining the evidence-based clinical steps with the required process and system changes, so that care is consistent for each patient. Logistical processes as well as clinical steps are optimized for each patient, so that postoperative recovery is quickened and complications, adverse events, and morbidity are reduced.

The overarching principles of an orthopedic ERAS pathway can be divided into four stages. At the preoperative stage, the focus is on optimization of preoperative health (such as the management of anemia and the promotion of smoking cessation), preoperative education and counseling, and the preemptive organization of discharge arrangements. Intraoperatively, atraumatic surgical techniques are used; anesthesia and analgesia protocols are optimized; multimodal opioid-sparing analgesia regimes are adopted; blood loss is spared; normovolemia and normothermia are promoted; and hypoxia is prevented. Postoperatively, early ambulation is encouraged; effective analgesia is given, avoiding opioids where feasible; catheters, drains, and drips are not used or removed as soon as possible; and patients are encouraged to eat and drink early and wash, dress, and socialize as soon as possible. All patients are discharged home, using agreed criteria managed by the multidisciplinary team, with clear instructions and support on progressing independently. The details of effective ERAS programs have been previously reported [2].

ERAS pathways have been so successful in reducing length of stay that there is now growing evidence to suggest that outpatient surgery for THA and TKA is feasible for selected patients. A recent prospective study [6] found that of 557 unselected patients who were referred for surgery, actual discharge on the day of surgery occurred for 13–15%. Fifty-four percent had been identified as potentially being eligible for outpatient surgery. Twenty-eight percent of THA patients who had been identified as being eligible went on to have outpatient surgery, along with 24% of identified TKA patients. It was noted that 25% of those originally identified as being eligible for outpatient surgery could not be discharged on the same day as they had no adult available to stay with them for more than 24 hours following discharge. The most common reasons for not being discharged were lack of motivation, not fulfilling discharge criteria, and inability to mobilize safely.

Two recent systematic reviews [7, 8] also suggest that outpatient arthroplasty can be a safe and effective procedure for carefully selected patients; however, more research is required in order to critically examine its safety and potential cost savings.

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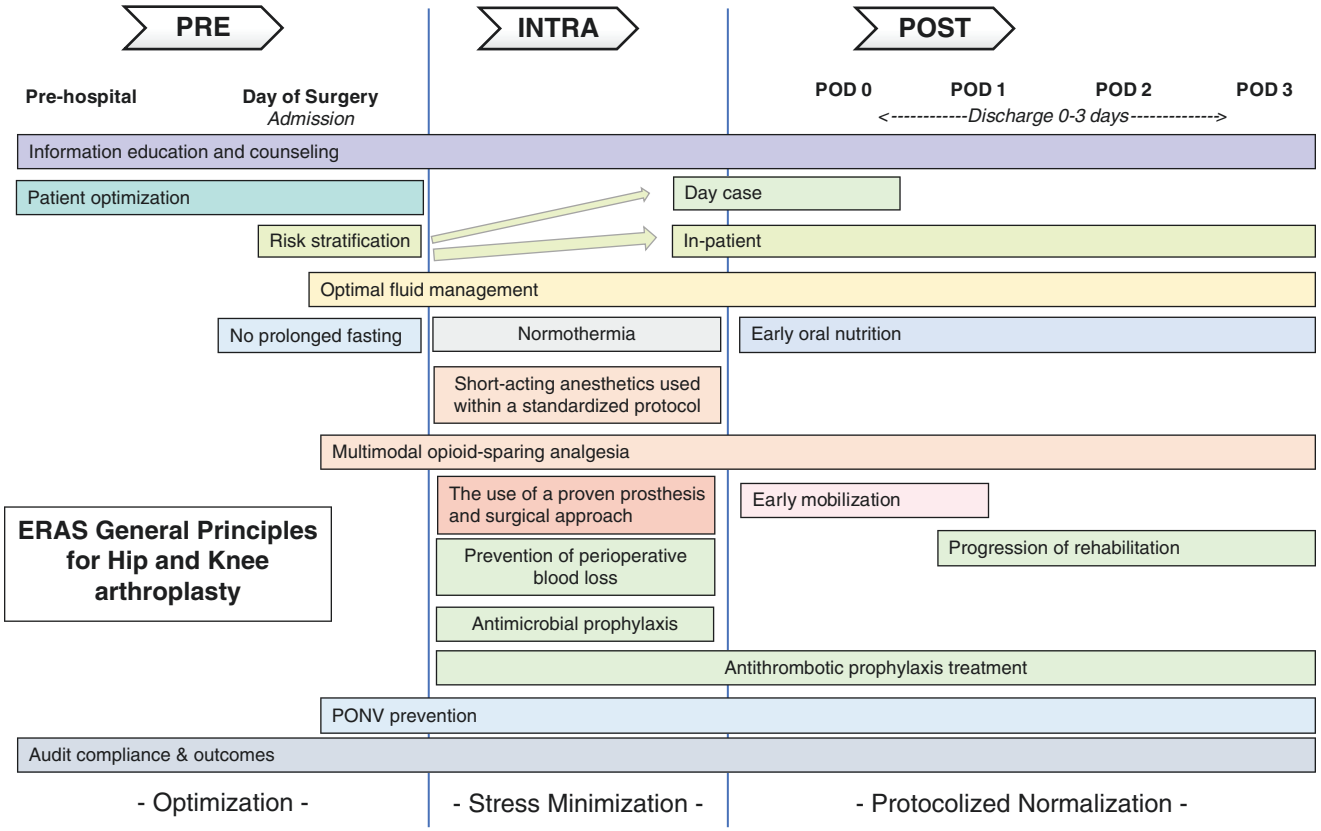

Fig. 49.1 ERAS general principles for hip and knee arthroplasty. PONV postoperative nausea and vomiting

ERAS in Total Hip Arthroplasty and Total Knee Arthroplasty

Clinical Outcomes

ERAS has been reported to improve the quality of care for patients in orthopedic surgery across a range of quality outcome measures, and it should be remembered that fast-track and ERAS protocols have always been based on the concept of "first better – then faster." Quality in healthcare is complex and multifaceted; however, the six dimensions through which the overall concept of quality is usually expressed (safety, effectiveness, patient-centeredness, timeliness, efficiency, and equity) can all be argued to have been improved through the implementation of ERAS within THA and TKA pathways.

Length of Stay, Readmissions, and Complications

Total hip arthroplasty (THA) and total knee arthroplasty (TKA) are common major surgical procedures often performed in older patients with complex comorbidities. ERAS has evolved during the past 20 years and has been shown to be effective in reducing length of hospital stay (LOS) from 4–12 days to 1–3 days [9, 10] without increasing complications or readmission rates or compromising patient safety [11]. In one of the most comprehensive reports of readmissions post ERAS in hip and knee arthroplasty, Husted et al. [2] found that in fast-track protocols, there was no increase in readmission rates and complications, such as dislocation after THA and reduced range of motion after TKA requiring manipulation.

The literature has been consistent in finding that readmissions do not increase following the implementation of ERAS; however, studies should be read carefully to ensure classification of readmissions is provided. In addition, the comparison of readmission rates after ERAS between different countries and institutions is difficult because readmissions may be classified differently. For example, a suspected deep vein thrombosis (DVT) patient may be admitted to hospital in some hospital systems or seen as an outpatient in others. Some patient groups are still more likely to be readmitted than others, even with ERAS; for example, a study of 2734 hip arthroplasty patients on a fast-track pathway found that patients aged 75 and over, and with pharmacologically treated psychiatric disease, were at an increased risk of dislocation [12]. In another study, the same research group concluded that surgery-related falls and subsequent readmission

after both hip and knee arthroplasty were related to patient characteristics rather than the fast-track pathway [13].

Mortality

Historically, mortality rates in hip and knee arthroplasty surgeries are relatively low, but the implementation of ERAS has been found to further reduce mortality rates. A large and well-conducted UK study comparing 3000 unselected ERAS patients with 3000 who had been on a traditional protocol reported reductions in mortality [10]. Mortality at 30 days and at 90 days was 0.1% and 0.5%, respectively, as compared to 0.5% and 0.8% when patients were on a traditional protocol ($p = 0.03$ and $p = 0.1$). A follow-up to this study [14] reported a mortality rate of 2.7% at 2 years, compared to 3.8% for those on the traditional protocol ($p = 0.05$). The authors suggest that a reduced stress response, shorter length of stay (LOS), and improved pain control for the ERAS cohort may have contributed to this lower rate. Importantly, in another large study of THA and TKA patients in Denmark, in which more than 17,000 on an ERAS pathway were compared to nearly 62,000 on a traditional pathway, no increase in mortality was found following ERAS, although this study fell short of proving a decrease in mortality within 90 days of surgery [11].

Patient-Reported Measures

Patient-reported outcome measures (PROMs) and patient-reported experience measures (PREMs) are considered an important patient-centered measure of quality within ERAS pathways [15, 16]. In the United Kingdom, hospitals are now required to collect PROMs for all primary total hip and knee arthroplasty patients as part of a national monitoring program. In the United Kingdom, the measures used comprise generic (e.g., EQ5D-5 L, EQ-VAS) and condition-specific measures (e.g., Oxford hip and knee scores).

A systematic review of patient-generated data following orthopedic surgery [17] for patients on an ERAS pathway found a lack of data. Their review included data on 2208 THR and TKR patients, from 8 papers. Six of the papers reported on patient satisfaction and found that scores were high and not affected by length of stay. Quality of life, reported in two papers, continued to increase following surgery for up to 12 months; however, one paper highlighted problems for patients in gaining necessary support post-discharge.

There are, however, issues in using PROMs as an outcome when assessing function. In a recent study of 80 patients [18], no correlation was found between objectively assessed function and improvements found using PROMs at 14 days post-surgery for THA patients and at 21 days post-surgery for TKA patients. While PROMs had improved following surgery, functional ability was decreased when objectively assessed using the 40 m paced walk test, a 30s chair stand test, and a 9-step stair-climb test and by an actigraphy recording of the level of activity. Consequently, in the future, objective functional data will be increasingly important from both a population and economic perspective, given the known increased healthcare costs and lower income levels of patients after THA and TKA [19], especially in light of recent research that has found little evidence that physical activity increases following TKA or THA [20–22].

Economics

Economic considerations are important when considering THA and TKA. They have been quoted to be two of the most successful operations and hence are being performed with increasing volume year-on-year around the world in order to reduce pain and improve function [23]. Although ERAS pathways have been shown to reduce LOS without increasing complications and readmissions, few studies have investigated the cost-effectiveness of implementing these protocols. A systematic review evaluating the cost-effectiveness of ERAS across a variety of surgical specialties concluded that ERAS protocols appeared to be cost-effective in the short term; however, data on costs post-discharge were lacking [24].

A study in Denmark [25] used a time-driven activity-based costing method to analyze time consumed by different staff members involved in the treatment of THA and TKA patients on ERAS pathways at two different hospitals. They found costs (excluding the prosthesis) of $2511 for THA and $2551 for TKA. Although these costs were not directly comparable to those published for more conventional pathways [26, 27] due to differences in process and logistics, importantly the ERAS pathways were cheaper.

Implementation

ERAS pathways have been shown to safely reduce length of stay to between 1 and 3 days, and outpatient surgery is now possible in unselected patients [6]. However, despite this there is evidence that only 40% of hospitals detail ERAS in patient information leaflets for THA and TKA [28], suggesting that adoption of the practice may not be complete. Therefore, in addition to further examine how to optimize the pathophysiological challenges that may affect early patient recovery, the present state of the implementation of ERAS in clinical practice should be considered. This is pertinent, because in order to achieve the goal of a "pain- and risk-free

surgery," we need to combine clinical evidence with implementation in order to do "the right things right" (Fig. 49.2). However, despite the established evidence-based and widespread acceptance of ERAS for THA and TKA principles over the last 20 years, mean LOS for both THA and TKA is still greater than 4 days in a socialized health system such as the National Health Service (NHS) in the United Kingdom [29]. The reasons that may underpin the slow adoption of ERAS have been previously described [30] and include a lack of understanding, a lack of acceptance, a lack of ability, no organizational will to change, deficient leadership, and poor audit mechanisms. Therefore, the immediate challenge for health systems such as the NHS to improve surgical outcomes is a quality improvement one, where efforts to implement what is already known should be prioritized given the improvement seen in clinical outcomes with ERAS.

The Development of ERAS® Society Guidelines for Hip and Knee Arthroplasty

Over the last 15 years, the systematic implementation of ERAS pathways has shown that hospital LOS and complications can be reduced [1] for a number of surgical procedures and ERAS protocols have been published for rectal, urological, pancreatic, gastric, breast and reconstructive, head and neck cancer, bariatric, and liver surgery [31–38].

For hip and knee arthroplasty, up until now there have only been narrative reviews on fast-track/enhanced recovery protocols [39–41], and a systematic and evidence-based guideline has just been produced [42]. The ERAS® Society recently brought together a group of international ERAS experts, in order to produce ERAS® Society recommendations for hip and knee arthroplasty. These recommendations [42, 43] represent an extremely important document in summarizing the large volume of heterogeneous studies across all ERAS components within hip and knee arthroplasty surgery. The recommendations are detailed in Table 49.1 and are represented schematically in Fig. 49.2. Many of the principles are consistent with the core principles of ERAS in other surgical procedures.

These guidelines include a total of 17 topic areas. Best practice includes optimizing preoperative patient education, anesthetic technique, and transfusion strategy, in combination with an opioid-sparing multimodal analgesic approach and early ambulation. There is insufficient evidence to recommend that one surgical technique (type of approach, use of a minimally invasive technique, prosthesis choice, or use of computer-assisted surgery) over another will independently effect achievement of discharge criteria. The guidelines are consistent with other ERAS surgical procedures in recommending the limitation of fasting preoperatively, along with intraoperative optimization of fluid management, maintenance of normothermia, and prophylactic treatment for

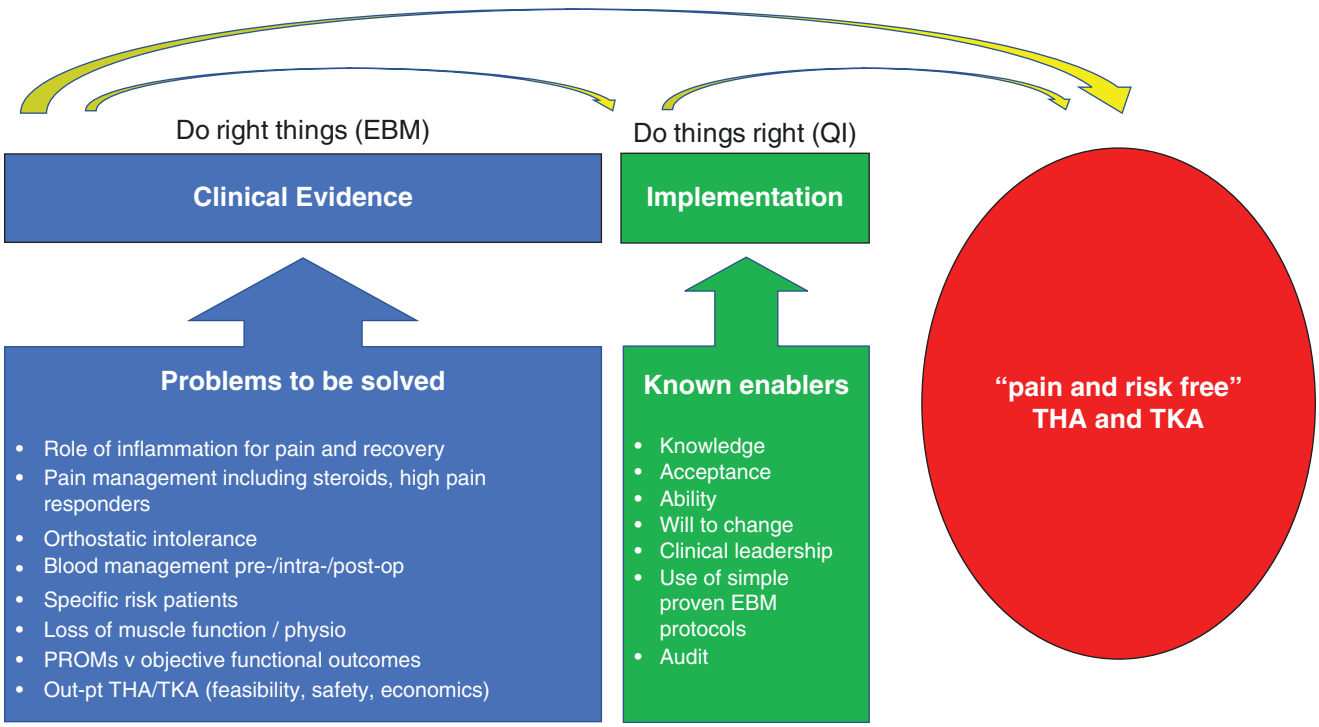

Fig. 49.2 ERAS in hip and knee replacement (THA and TKA): Recommendations for future development. EBM evidenced-based medicine, QI quality improvement, PROMs patient-reported outcome measures, Out-pt outpatient

Table 49.1 ERAS® Society recommendations for hip and knee arthroplasty

Number	Item	Recommendation	Evidence level	Recommendation grade
1	Preoperative information education and counseling	Patients should routinely receive preoperative education	Low	Strong
2	Preoperative optimization	4 weeks or more smoking cessation is recommended prior to surgery. Alcohol cessation programs are recommended for alcohol abusers	Smoking: high Alcohol: low	Strong
		Anemia should be actively identified, investigated, and corrected preoperatively	High	Strong
3	Preoperative fasting	Clear fluids should be allowed up to 2 h and solids up to 6 h hours prior to induction of anesthesia	Moderate	Strong
4	Standard anesthetic protocol	General anesthesia and neuroaxial techniques may both be used as part of multimodal anesthetic regimes	General anesthesia: moderate Neuroaxial techniques: moderate	Strong
5	Use of local anesthetics for infiltration analgesia and nerve blocks	Within a multimodal opioid-sparing analgesic regimen, the routine use of LIA is recommended for knee replacement but not for hip replacement. Nerve block techniques have not shown clinical superiority over LIA	LIA in knee replacement: high	Strong
6	Postoperative nausea and vomiting	Patients should be screened for and given multimodal PONV prophylaxis and treatment	Moderate	Strong
7	Prevention of perioperative blood loss	Tranexamic acid is recommended to reduce perioperative blood loss and the requirement for postoperative allogenic blood transfusion	High	Strong
8	Perioperative oral analgesia	A multimodal opioid-sparing approach to analgesia should be adopted. The routine use of paracetamol and NSAIDs is recommended for patients without contraindications		
			Paracetamol: Moderate	Strong
			NSAIDs: High	Strong
9	Maintaining normothermia	Normal body temperature should be maintained peri- and postoperatively	High	Strong
10	Antimicrobial prophylaxis	Patients should receive systemic antimicrobial prophylaxis	Moderate	Strong
11	Antithrombotic prophylaxis treatment	Patients are at increased risk of VTE and should undergo pharmacologic and mechanical prophylaxis in line with local policy	Moderate	Strong
12	Perioperative surgical factors	Surgeons are recommended to use a proven prosthesis and surgical approach	High	Strong
13	Perioperative fluid management	A fluid balance should be maintained to avoid over- and under-hydration	Moderate	Strong
14	Postoperative nutritional care	An early return to normal diet should be promoted	Low	Strong
15	Early mobilization	Patients should be mobilized as early as they are able in order to facilitate early achievement of discharge criteria	Moderate	Strong
16	Criteria-based discharge	A team-based functional discharge criteria should be used to facilitate patient discharge directly to their home	Low	Strong
17	Continuous improvement and audit	The routine audit of process measures, clinical outcomes, cost-effectiveness, patient satisfaction/experience, and changes to the pathway is recommended	Low	Strong

LIA local infiltration analgesia, *PONV* postoperative nausea and vomiting, *VTE* venous thromboembolism

infection and thrombosis. Postoperatively, in addition to early mobilization, early oral feeding is recommended. The published guidelines [43] will provide a detailed narrative review of all of the current literature and explain why certain components have been included and why other elements are not currently recommended.

The recommendations provide a starting point for implementation for teams new to ERAS and as a point of reflection for experienced ERAS teams to examine their current practice. These guidelines and the testing of their implementation, as has been performed in other ERAS procedures, will hopefully allow us to consolidate consensus within the evidence base, and generate new evidence, through systematic prospective data collection and through clinical trials.

Future Directions for Research

Future research for ERAS in hip and knee arthroplasty should focus on reaching the goal of the "pain- and risk-free"

hip and knee arthroplasty [44]. In order to do this, we need to better understand the pathophysiological mechanisms of recovery and the potential to optimize post-discharge functional outcomes [45]. This will be important because for some of the ERAS components, there is a strong need for properly designed randomized controlled studies that are sufficiently powered and performed in ERAS settings and that allow for discrimination between outcome parameters.

More specifically, it has been identified by Wainwright and Kehlet [45] that future trials should examine the preoperative prediction of high-inflammatory responders, with further dose-finding or repeat-dosing glucocorticoid or other anti-inflammatory agents in studies in high-inflammatory responders [46] as well as more specific studies on high-pain responders (preoperative opioid users, pain catastrophizers, sensitized patients, etc.) [47].

In addition, work is still required in order to understand how to reduce impairment of physical activity and improve function quicker postoperatively; how to better identify patients at high risk of complications owing to psychiatric disorders, chronic renal failure, and orthostatic intolerance; anemia and transfusion thresholds; postoperative urine retention and urinary bladder catheterization; and how to improve sleep. Intertwined with this will be the need for further research on the feasibility of same-day surgery and the type, timing, and duration of physiotherapy post-discharge [45, 48]. The future directions recommended for research are summarized within Fig. 49.2 along with the recognized implementation factors identified earlier in the chapter.

ERAS in Other Orthopedic Procedures

Given the excellent outcomes for ERAS in hip and knee arthroplasty patients, it would therefore seem prudent to apply ERAS to every orthopedic procedure so that all orthopedic patients may benefit from the approach. Given the high volumes of orthopedic procedures, there is significant scope to improve patient outcomes and also significantly increase hospital productivity if ERAS pathways are implemented more widely. The staff involved in treating and looking after joint arthroplasty patients are often the same teams that care for all other types of orthopedic patients. Therefore, it should be relatively straightforward to achieve strong commitment and "buy-in" from these people to change the pathway and improve patient outcomes for other procedures.

Fractured Neck of Femur

Despite the fact that fractured neck of femur (FNOF) is an emergency procedure, given the similarities to primary and revision hip arthroplasty and the substantial scope for improvement, the application of ERAS to this population demands attention. The National Hip Fracture Database reports that in 2016 more than 65,000 people were treated for hip fracture in England, Wales, and Northern Ireland. A study of NHS Trusts in England from November 2013 to October 2014 found that LOS for NHS Trusts ranged from 12.3 days to 33.7 days, even though predicted LOS for these NHS Trusts, when adjusted for case mix, only ranged from 21.5 to 24.4 days [49]. Other studies have also found significant variation in practice in the treatment and care of trauma patients [50, 51]. Wainwright et al. [49] contend that the introduction of an adapted and FNOF procedure-specific ERAS pathway could reduce variations in practice and therefore overall LOS.

As with other orthopedic procedures, pain is a major contributor to delayed mobilization and recovery in FNOF patients, and Wainwright et al. [49] highlighted the role that peripheral nerve blocks may have in this pathway. A recent Cochrane Review found that compared with other modes of analgesia, peripheral nerve blocks used to treat FNOF reduce pain on movement better within 30 minutes, the risk of postoperative pneumonia is reduced, there is a reduced time to first mobilization after hip fracture surgery (approximately 11 hours earlier), and the use of a peripheral nerve block given as a single injection leads to a reduced cost of analgesic drugs [52].

A further study in New Zealand [53] supports the implementation of ERAS for this patient cohort, showing that overall LOS reduced for FNOF patients by 4 days after the introduction of an ERAS pathway. Time in the emergency department was reduced by 30 minutes, and the overall time in rehabilitation reduced by 3–7 days depending on the type of facility, so that patients spent 95 hours less in hospital than a comparable group on a conventional pathway in the 3 years prior to the ERAS pathway introduction. The FNOF-specific ERAS pathway focused on full interdisciplinary involvement. Orthopedic assessment was encouraged on the orthopedic ward that specialized in FNOF management, rather than in the emergency department, and every possible attempt was made to operate on the patient either that day or the following morning. Outstanding investigations were prioritized so that patients could proceed to surgery quickly. It was agreed that all patients should be suitable for rehabilitation and weight bearing 48 hours following surgery. The rehabilitation team was multidisciplinary, comprising nurses, medical, occupational therapists, physiotherapists, and social workers. Electronic data on the management of the patients was available in real time and was analyzed by staff on a weekly basis so that cross-functional teams could explore process issues and agree on actions to continue to improve clinical outcomes. A second study by Haugan et al. [54] in Norway, comparing 1032 FNOF patients on an ERAS protocol to 788 on a conventional pathway, found no differences

between the groups in mortality and readmission within 365 days after the initial hospital admission. LOS was also reduced by 3.4 days in the ERAS group.

The findings of these initial studies on using ERAS pathways in FNOF are encouraging. If the success of implementing ERAS in elective pathways can be reproduced in FNOF pathways, this would have a big impact on health systems in terms of resources and cost economics and help to reduce some of the capacity and economic pressures on these systems.

Shoulder Arthroplasty

Total shoulder arthroplasty (TSA) is becoming increasingly popular, with the United States (US) reporting an increase in procedure rates of 319% between 1993 and 2007 [55]. As yet, there are few studies reporting on ERAS concepts being applied to TSA. An examination of Hospital Episode Statistics [56] from April 2015 to March 2016 found that NHS Trusts in England had LOS that varied from 1.0 to 6.4 days for TSA [57]. Expected case mix-adjusted LOS ranged from 10.0 to 3.9 days, thereby suggesting that there is scope to reduce LOS for TSA with the introduction of ERAS.

As with all types of surgery, procedure-specific guidance will be required for ERAS in TSA, whereby principles from THA/TKA are adapted and added to TSA. One such example is in the multimodal pain management strategies that have been successfully adapted and implemented in TSA pathways [58, 59]. Routman et al. [60] found that the addition of intravenous dexamethasone and liposomal bupivacaine injections to the surgical site intraoperatively in patients undergoing TSA under general anesthesia, with a single-injection interscalene block, reduced median LOS from 2 days to 1 day, with reductions in pain and the need for opioids. As with other orthopedic surgeries, conflicting results have been found on the most effective combination of regional blocks [61, 62] in total shoulder arthroplasty (TSA).

A US retrospective study [63] matched 136 TSA patients in a tertiary referral center (TRC) to 136 patients at an orthopedic specialty hospital (OSH) with protocols similar to ERAS. They found that although readmission rates were similar, the OSH had a lower LOS than the TRC (1.3 ± 0.5 days vs 1.9 ± 0.6 days, $p < 0.001$). Previously a study in Germany [64] had introduced ERAS concepts in areas such as pain management, drainage and catheter management, physiotherapy, and early mobilization and found improvements in LOS and patient and staff satisfaction.

Recent research, mostly retrospective, also indicates that outpatient TSA, implementing ERAS concepts such as multimodal pain strategies and minimizing blood loss, is feasible in appropriately selected patients [65, 66].

Ankle Arthroplasty

Until recently arthrodesis has been the routine treatment for end-stage osteoarthritis of the ankle. However total ankle arthroplasty (TAA) is now becoming more common with the introduction of better surgical techniques and training and a third generation of three-component mobile-bearing implants [67, 68]. Hospital Episodes Statistics (HES) data from NHS Trusts in England from April 2015 to March 2016 show that the mean LOS for TAA was 3.3 days, with a staggering range of 17.3 days between the hospitals with the minimum and maximum mean LOS [69]. The range of case mix-adjusted expected LOS was just 3.7 days, suggesting that those hospitals with a longer LOS were not outliers due to case mix but due to the pathway of care, and so therefore improvements may be possible with the introduction of ERAS.

There is little in the literature on the application of ERAS concepts to TAA. However, there is some evidence supporting the use of regional anesthesia and analgesia over systemic opioids [70–72], and pain management is a vital consideration in TAA patients. However, as yet there is limited evidence on multimodal pain management as part of ERAS pathways for TAA. One recent small study gave patients 30–50 ml of bupivacaine as local infiltration analgesia (LIA) intraoperatively as part of a newly introduced ERAS pathway. LOS reduced from 3.6 to 2.3 days, and there was a significant improvement in pain scores following the introduction of the new pathway [73]. There have been some small retrospective studies on outpatients undergoing TAA that have used a single-shot popliteal block with ropivacaine followed by periarticular liposomal bupivacaine at the end of the surgery [74] or a popliteal and saphenous nerve block prior to surgery [75]; however further research is required in this area.

These studies therefore provide evidence to suggest that outpatient TAA can be successful for selected patients, if teams are experienced and if there is a good postoperative support network [75, 76]. Further work is required, especially within rehabilitation where discharge can be delayed due to social/home circumstances, and post-discharge rehabilitation improvements are required in order to expedite return to functional activities.

Spinal Surgery

The demand for complex spinal surgery is increasing [77, 78] and may be undertaken within both orthopedic and neurosurgical settings. Wide variations in LOS, complications rates, postoperative pain, and functional recovery are reported [77, 79], and so, as for TSA and TAA surgeries, there are strong clinical and economics arguments to improve

outcomes for spinal surgery by implementing ERAS principles.

There is little evidence as yet published on the implementation of ERAS pathways in spinal surgery [80]. The introduction of a novel minimally invasive surgical approach with ERAS components [81] for 42 patients undergoing one- or two-level spinal fusion was found to be successful. A quality improvement study [82] examined the development of an ERAS pathway in an elective spinal service, in a hospital experienced in implementing ERAS for hip and knee arthroplasty patients. The service included more complex procedures, such as posterior scoliosis correction. ERAS components of the pathway included a leaflet describing what to expect following surgery, carbohydrate drinks, laxatives, minimally invasive surgical techniques, the use of tranexamic acid for longer operations, and an estimated discharge date. Standardized multimodal anesthetic and analgesic regimens were implemented, avoiding large doses of intraoperative opioids. The ERAS pathway was successful with overall mean LOS reduced by 3 days to 3 days and readmissions reduced to 3% from 7%. In addition, nearly all patients rated their satisfaction with the pathway as good or excellent. Studies have also shown that ERAS pathways can be successfully implemented for adolescent idiopathic scoliosis surgery [83, 84].

These initial successes indicate that ERAS pathways should be applicable to all spinal surgery patients, although there is a need for spinal-specific guidelines to enable more widespread adoption. These guidelines need to allow for adaptation to different procedures and the varying levels of preoperative disability and pain [42]. A dedicated chapter on spinal surgery and neurosurgery, providing more details of this patient group, can be found in this book.

Conclusion

This chapter has detailed that ERAS is a proven and widely adopted technique for improving outcomes in hip and knee arthroplasty. While outcomes have improved dramatically in the last 10 years, challenges remain in order to achieve widespread adoption and implementation of what is already known, and there are future research challenges in order to improve our understanding of the pathophysiology of factors effecting recovery, such as the inflammatory response and pain, and the most effective rehabilitation regimes. The new ERAS Guidelines will hopefully help to bridge both the implementation gap for those new to ERAS and help to consolidate the current heterogeneous evidence base, where direct comparison of ERAS components is difficult with so many differences to the ERAS pathways currently used. The application and development of ERAS in other elective and emergency orthopedic procedures is an exciting and emerging area that looks set to bring the benefits of ERAS to even more patients.

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ERAS in Otolaryngology-Head and Neck Surgery

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Joseph C. Dort

Background

Modern healthcare is the best we have ever seen. Life expectancy for men and women in the Western world is now more than 80 years, and mortality from major diseases such as heart disease, stroke, and cancer continue to improve. Modern surgery, when combined with anesthesiology and intensive care, delivers outstanding outcomes for many patients. Yet, despite these encouraging results, there are problems with the design, delivery, and effectiveness of clinical care. Variation in the design and delivery of healthcare is a longstanding and well-known problem [1, 2]. In the surgical realm, over- and underutilization of surgical procedures are common, and variation in perioperative care is frequently observed. In 2000 and 2001, the Institute of Medicine (IOM) published two reports highlighting the frequency of serious adverse events in American hospitals and also proposed solutions to these problems [3–5]. A subsequent national study found similar outcomes in the publicly funded Canadian healthcare system [6], suggesting that these problems were not confined to a single-country or healthcare system. It is also evident that many of these challenges are not due to lack of knowledge but rather a failure to translate what we know into practice [7].

Why does modern healthcare fail to meet our own and our patients' expectations? Many blame the "culture" of medicine as a root cause, but the reasons are more complex. Medical knowledge expands at a rate far beyond the human brain's ability to acquire it, and therefore systems that support the delivery of "best care" or "evidence-based care" are one potential solution to inappropriate variation and the knowledge translation gap. This chapter will explore the development of pathways and protocols that support delivery of surgical care and examine the results arising from their use. The chapter will focus on ORL, but knowledge and evidence from other surgical areas will also be used to illustrate the value of coordinated, team-based care. Special attention will be paid to enhanced recovery after surgery (ERAS) protocols as a means of optimizing perioperative care and improving clinical outcomes.

Care pathways and clinical protocols have been published since the early 1990s. Early experience using these tools came from Intermountain Healthcare as well as other centers [8]. What constitutes a care pathway is also an important consideration. For this chapter a care pathway is defined as a tool that defines specific interventions and timelines for a particular group of patients. Furthermore, a care pathway must also incorporate a measurement, audit, and feedback mechanism so that providers know the results of their clinical interventions. The feedback system is also useful for modifying and improving pathways based on data. Because care pathways are time-consuming and expensive to design, deliver, and maintain, it is important to select high-priority clinical processes for their application [9].

Otolaryngology-head and neck surgery (ORL) is a broad surgical specialty in which many patients are managed on an outpatient or same-day surgery basis. These types of day surgery procedures are probably not the highest priority for enhanced recovery protocols. On the other hand, major head and neck surgery with free flap reconstruction represents an area of ORL practice that is complex, costly, time-consuming, and potentially harmful. Patients undergoing these major oncologic procedures frequently have hospital lengths of stay (LOS) of 14 days or greater. Recognizing this need, in 1997 Cohen et al. published the first study investigating the use of a care pathway in the management of patients undergoing major head and neck surgery [10]. The authors showed significant improvements in LOS and costs in a diverse group of head and neck surgery patients. In addition to these benefits, the authors also commented on the positive impact of their pathway on team collaboration and the organization and delivery of care. Another study of laryngectomy patients showed similar improvements in LOS and healthcare costs

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[11]. Patients requiring flaps were excluded from this study. In a 1999 study, Husbands and colleagues looked at a pathway-treated cohort compared to a non-pathway-treated group [12, 13]. LOS and costs were reduced, although few details of the actual pathway were published. A study of patients undergoing neck dissection showed improved LOS in pathway patients compared to a historical cohort but, interestingly, no difference when compared to a contemporaneous non-pathway group [14].

In the first 4 years of the new millennium, seven publications focused on the impact of pathways on recovery from head and neck oncologic procedures [12, 14–19]. Each of these studies stated different benefits including better team satisfaction, reduced LOS, and reduced costs of care. Yueh's 2003 study had an interesting design in which he compared two hospitals—one pathway hospital and one non-pathway hospital—and concluded that a care pathway did not impact LOS [19]. However, this study excluded complicated patients, making the results difficult to interpret. The Calgary group published a series of studies showing the impact of care pathways on complications, tracheotomy management, and cost-effectiveness [20–23]. The Calgary program also demonstrated the association between care pathway-directed management of head and neck patients and post-discharge healthcare utilization [24], suggesting that pathway-directed treatment had benefits that persisted after discharge. In 2016 Gordon conducted a systematic review of head and neck care pathways and concluded that care pathways seemed to be a promising tool for reducing LOS and costs of care [24, 25]. However, study heterogeneity and overall low quality precluded formal meta-analysis or pooling of results.

Bater and colleagues published a study of an enhanced recovery protocol in head and neck surgery patients [26]. This study is the first to look at the impact of interventions on all three phases of surgical care (preoperative, intraoperative, and postoperative) in a cohort of head and neck patients undergoing resection with free flap reconstruction. The authors found a shorter LOS in the enhanced recovery group but no differences in complications. Protocol-treated patients tended to be younger and more likely to have a soft-tissue-only reconstruction. Yetzer et al. concluded care pathways were beneficial, but their study had significant design flaws, and the results may not be generally applicable [27].

What Is ERAS and How Does It Differ from Current Care Pathways in Head and Neck Surgery?

All of the studies discussed in the previous section illustrate that care pathways (CP) are a focus of interest and research in head and neck surgery. No prospective trials comparing pathway to non-pathway management have been published in the head and neck surgery literature, and such studies would be difficult to implement given the body of evidence that suggests pathway-managed patients have better outcomes. None of the current studies investigated a full ERAS program and its impact on clinical outcomes.

What, therefore, is the difference between a CP and ERAS? At a basic level, both CPs and ERAS are protocols that guide the nature and timing of care in a defined patient group. However, ERAS is founded on improving distinct phases of surgical care: preadmission, preoperative, intraoperative, and postoperative. ERAS protocols are designed to reduce the surgical stress response by optimizing patient education, using pre-habilitation where feasible, avoiding fasting and implementing preoperative carbohydrate loading, balanced fluid management, and multi-modal pain management so as to reduce postoperative nausea and vomiting. The principles and practice of ERAS were first developed and applied in patients undergoing colorectal surgery.

Henrik Kehlet, a Danish general surgeon, developed and published the initial concepts that resulted in "fast-track" protocols [28, 29]. Kehlet's work on fast track was further expanded by Fearon, Ljungqvist, and others who developed the concepts and protocols that are now recognized as ERAS. Extensive research shows the beneficial metabolic, physiologic, and clinical impacts that form the scientific basis of ERAS [30–32]. An international ERAS® Society was formally constituted in 2010, and ERAS has now spread to multiple surgical specialties including major head and neck surgery with free flap reconstruction. The details of ERAS in colorectal and other areas of surgery are extensively covered elsewhere in this book and will not be repeated here. The reader is encouraged to read these chapters to learn more.

Current ERAS Guideline for Major Head and Neck Surgery with Free Flap Reconstruction

The results of ERAS in colorectal and other surgical disciplines were extensively published after 2010. As this literature was assimilated, it became obvious that patients undergoing major head and neck surgery with free flap reconstruction were ideally suited to ERAS-guided care. It was clear from the literature and our own experience that designing and implementing care pathways for this patient population resulted in dramatic improvements in clinical and financial performance. It was therefore hypothesized that the additional care elements inherent in ERAS-guided care might result in further performance enhancement. In 2015 an international group of experts was formed from head and neck surgery, general surgery, anesthesiology, intensive care, nutrition, and literature synthesis. This head and neck working group approached the ERAS® Society,

and work began on creating an ERAS guideline for patients undergoing major head and neck resection with free flap reconstruction [33].

Methodology

The working group met regularly from May to November 2015. Group discussions were managed by a modified Delphi process, and consensus was reached in all discussions. Initially the group focused on understanding the usual ERAS care elements and determining the major areas where head and neck patients differed from other surgical populations. It was clear from the beginning that a simple "transplant" of ERAS from colorectal to head and neck surgery was neither feasible nor desirable.

The working group analyzed the various care processes inherent in managing patients undergoing head and neck resection and reconstruction and defined 17 crucial care elements that were necessary for an ERAS guideline. Some of the "standard" care elements—for example, preoperative teaching, fasting guidelines, and mobilization—were obviously beneficial for head and neck patients. However, other elements such as tracheotomy management, flap monitoring, donor site care, and others had to be customized for the head and neck surgical population.

After defining the care elements, an extensive, structured literature search was conducted, topics were assigned to group members, and the literature was evaluated using a standardized approach to quality assessment. After each topic was written, recommendations were formulated and debated by all team members. Several rounds of revision were required before consensus was reached. The final manuscript was drafted and submitted for publication. Detailed description of the methods can be found in the published consensus statement [33].

Guideline Summary

The care elements and recommendations are summarized in Table 50.1 [33]. One challenge faced by the working group was the relatively low-quality evidence found in the head and neck literature. Many of the studies found were retrospective,

Table 50.1 Enhanced recovery after surgery recommendations for perioperative care in head and neck cancer surgery with free flap reconstruction.

Item	Recommendation	Evidence	Recommendation
1. Preadmission education	All patients undergoing major head and neck cancer surgery with free flap reconstruction should receive structured teaching from a qualified health practitioner	Low	Strong
2. Perioperative nutritional care	All patients undergoing major surgery for head and neck cancer should undergo preoperative comprehensive nutritional assessment, with a special focus on dysphagia and risk for refeeding syndrome. Preoperative nutrition intervention is recommended for those identified as malnourished	High	Strong
	In patients for whom oral feeding cannot be established, postoperative tube feeding should be initiated within 24 hours. Nutrition interventions should be developed in consultation with the multidisciplinary team and individualized according to nutritional status and surgical procedure	Moderate	Strong
	Preoperative fasting should be minimized. In patients suitable for oral intake, clear fluids should be permitted for up to 2 hours, and solids for up to 6 hours, prior to anesthesia. Preoperative carbohydrate (CHO) treatment may be offered to head and neck cancer patients with appropriate screening and management for those presenting with dysphagia or risk of refeeding syndrome	High – fluids Low – solids Low – CHO	Strong – fluids Strong – solids Conditional – CHO
3. Prophylaxis against thromboembolism	Patients undergoing head and neck cancer surgery with free flap reconstruction are at increased risk of venous thromboembolism (VTE) and should undergo pharmacologic prophylaxis; however, the risk of bleeding must be weighed against the benefits on an individualized basis	High	Strong
4. Antibiotic prophylaxis	Perioperative antibiotics are not indicated for short, clean head and neck oncologic procedures. In clean-contaminated procedures, perioperative antibiotics should be given 1 hour prior to surgery and continued for 24 hours	High	Strong
5. Postoperative nausea/vomiting prophylaxis	Patients undergoing head and neck cancer surgery should receive preoperative and intraoperative medications to mitigate PONV. A combination of corticosteroid and antiemetic should be considered	High	Strong
6. Pre-anesthetic medication	Patients should not receive short-acting anxiolytics, given intravenously and titrated to required effect	High	Strong
	Multimodal analgesia, including paracetamol (acetaminophen), celecoxib, and possibly gabapentin, should be given to mitigate postoperative pain	High	Strong

(continued)

Table 50.1 (continued)

Item	Recommendation	Evidence	Recommendation
7. Standard anesthetic protocol	Patients should undergo airway assessment. General anesthesia is recommended; however, there is little in the literature to recommend a specific anesthetic regimen	Low	Strong
8. Preventing hypothermia	Normothermia should be maintained intraoperatively. Temperature monitoring is necessary to ensure normothermia is maintained	High	Strong
9. Perioperative fluid management	Fluids should be managed in a goal-directed manner, avoiding over- and under-hydration	Moderate	Strong
10. Routine postoperative intensive care admission	Routine ICU admission to facilitate an immediate postoperative period of deep sedation and artificial respiration should be avoided. A subset of low-risk uncomplicated patients may be managed safely after recovery from anesthesia on a high-dependency unit or specialist ward, provided adequate skilled nursing and medical coverage is provided	Low	Weak
11. Postoperative analgesia	Patient-controlled anesthesia is an efficient way to control postoperative pain and may be employed in patients undergoing head and neck cancer surgery. Multimodal analgesia approaches are also effective and can reduce the need for narcotic analgesics. No recommendation can be made on the role of additional nerve blocks	High	Strong
12. Postoperative flap monitoring	Free flap monitoring should be performed at least hourly for the first 24 hours postoperatively. Monitoring should be continued for the duration of the patient's stay, with tapering of intensity after the first 24 hours. Method of monitoring should include, at a minimum, clinical examination by staff experienced with free flap monitoring. Adjunct monitoring techniques should be considered	Moderate	Strong
13. Postoperative mobilization	Early mobilization, within the first 24 hours of surgery if possible, is recommended for patients undergoing major head and neck cancer surgery	Moderate	Strong
14. Postoperative wound management	Vacuum-assisted closure is recommended for complex cervical wounds.	High	Strong
	Vacuum-assisted closure may be considered for free flap donor site.	Moderate	Strong
	Polyurethane film or hydrocolloid dressings should be used for skin graft donor site management	High	Strong
15. Urinary catheterization	Urinary catheters should be removed as soon as the patient is able to void, ideally less than 24 hours after completion of surgery	High	Strong
16. Tracheostomy management	Decannulation after tracheostomy and stoma closure is recommended	High	Strong
	Surgical closure of the tracheostomy site is recommended	Moderate	Strong
17. Postoperative pulmonary physical therapy	Pulmonary physical therapy should be initiated as early as possible after head and neck reconstructions in order to avoid pulmonary complications	High	Strong

Reprinted with permission from Dort et al. [33]
PONV postoperative nausea and vomiting, *ICU* intensive care unit

often with smaller cohort sizes. This contrasted with the ERAS colorectal literature, which was more mature and therefore higher quality.

Nutritional assessment and optimization is believed to be an important aspect of head and neck care that, for a variety of reasons, is often neglected. Other elements such as venous thromboembolism prophylaxis, antibiotic prophylaxis intensive flap monitoring are common practices in most major head and neck programs and are all strongly recommended.

Standardizing anesthetic practices and coordinating these with multimodal analgesia and postoperative nausea and vomiting prophylaxis are important care elements that require a high level of communication and cooperation among members of the care team. Fluid management is similarly important and also requires close communication between the surgeon, anesthesiologist, and intensive care unit (ICU). Goal-directed fluid therapy is one approach to managing fluid balance intraoperatively but has not been well studied in the head and neck population.

It was apparent from the working group and from the literature that there is significant variation in pain management protocols for head and neck patients. Most programs rely heavily on narcotics to control pain and few currently use multimodal analgesia protocols. Mobilization is another area where considerable variation exists. The working group felt that, despite the lack of strong evidence for mobilization, this patient group should be mobilized within the first 24 hours after surgery. Mobilization is important in reducing pulmonary complications, contributes to patient well-being, and enables an early transition to self-care. Early removal of urinary catheters reduces the risk of urinary tract infection and also facilitates early mobilization.

Tracheotomy care is important in this patient population, and there is wide variation in tracheotomy management. Working group members all agreed that tracheotomy removal as soon as feasible is a good strategy for reducing complications and enabling early discharge. Early suturing

of the tracheotomy site is also a simple method of enhancing swallowing and wound healing after decannulation.

Approaches to Implementation

Creating and publishing a guideline provides the intellectual framework for improving care and is an important first step toward changing practice. However, implementing a guideline into routine clinical workflow is challenging and requires a coordinated multidisciplinary approach [34]. ERAS has been used for colorectal surgery for 5 years in the Province of Alberta, Canada, and was implemented at multiple sites across the province [35, 36]. The Alberta colorectal experience developed an approach that guided implementation in other Alberta surgical disciplines. Support for measurement, audit, and feedback is an important part of the implementation plan. The ERAS interactive audit system (EIAS) is a commercial product developed to collect, analyze, and report colorectal surgical data based on ERAS® Society developed guidelines. EIAS has been modified to support other surgical disciplines, and a head and neck surgery module is now available. Gramlich and colleagues emphasize the importance of teamwork and timely feedback in making ERAS implementation successful [35].

Application to Practice and Early Results

As outlined in the Background section of this chapter, few head and neck surgery programs have long-term expertise with care pathway development and implementation. In Calgary the group had 8 years of experience using a postoperative care pathway that includes a prospective measurement, audit, and feedback system. This background proved to be a useful platform to launch a full ERAS program. Other programs with similar experience are also well-prepared to make the transition to ERAS.

Since the publication of the head and neck consensus statement, the Guidelines group has worked collaboratively to customize a head and neck version of EIAS. The full head and neck ERAS program has been in operation at the Foothills Medical Centre (FMC) in Calgary since December 2017. Although a postoperative pathway was fully functional for many years, FMC did not have formal protocols for preoperative management, multimodal analgesia, and intraoperative fluid management. Developing these aspects of ERAS required meetings, presentations, and focus group sessions with a full range of providers. Patient feedback was also sought and integrated into the process. Intensivists and anesthesiologists were actively involved in ERAS development, and several iterations of the protocol were required before consensus was achieved. Finally, in order to facilitate their adoption, the protocols and processes were translated into surgical booking forms and computerized order sets.

Patients are identified as "ERAS eligible" at their first visit with a surgeon. Preoperative orders and processes specific to ERAS are then implemented, and preoperative teaching occurs in the preoperative assessment clinic so that patients are familiar with ERAS. Modern fasting guidelines and instructions for carbohydrate loading are also reviewed at that visit. Prior to coming to the operating room, patients are administered acetaminophen and a nonsteroidal anti-inflammatory drug (NSAID) as well as a gabapentinoid. In patients with compromised renal function, the NSAID is withheld. At the present time, FMC does not have a formal "prehabilitation" program for head and neck patients, but such a program is being planned. Intraoperative ERAS interventions are discussed during the presurgical safety briefing so that the surgical and anesthesiology teams can discuss the intraoperative and early postoperative management plan and identify any areas requiring clarification. Postoperatively most patients are sent to the intensive care unit for overnight monitoring, and in the majority of cases, patients are fully awake and do not need ventilation. Postoperative care is managed on a dedicated head and neck nursing unit. The overall workflow followed for an ERAS head and neck patient is summarized in Figs. 50.1 and 50.2.

Preliminary results after the first 7 months of ERAS implementation are promising. However, there are too few data to draw meaningful conclusions about ERAS impact compared to our standard postoperative care pathway. Also the EIAS system is significantly different than our current audit system, and we are working to adapt and learn the nuances of EIAS. Between December 2017 and June 2018, a total of 34 patients were enrolled in the head and neck ERAS program. All patients underwent major head and neck resection with free flap reconstruction. ERAS patients were compared to a baseline cohort of 50 patients who had similar procedures between September 2016 and September 2017. The average age of the baseline cohort was 61.4 years, and 80% were males. The average age of the ERAS cohort was 61.9 years, and 62% were males.

Table 50.2 shows overall and item-specific compliance for several ERAS measures, and overall compliance is improving. Furthermore, some of the poor compliance outcomes in the baseline group are due to missing documentation and evolving operational definitions within EIAS.

The median length of hospital stay (LOS) was 12 days pre-ERAS and 10 days in the ERAS group. The ERAS group had fewer patients requiring tracheotomy, which reduced the overall LOS in this group. Our ERAS implementation is at a very early stage, and more work is needed on data collection, analysis, and feedback.

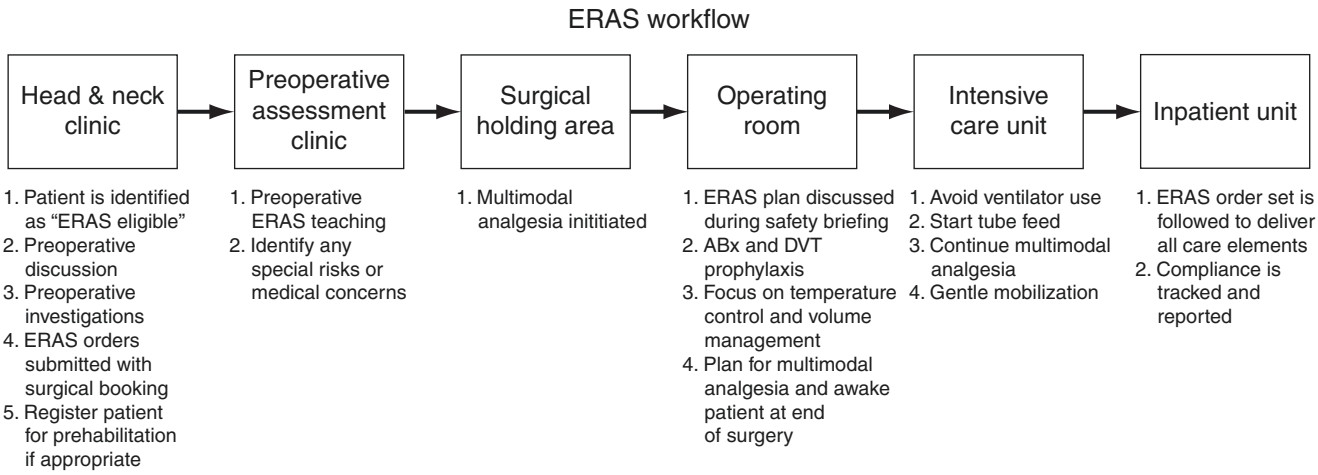

Fig. 50.1 Overview of ERAS head and neck workflow summarizing main activities taking place at each checkpoint along the patient's path

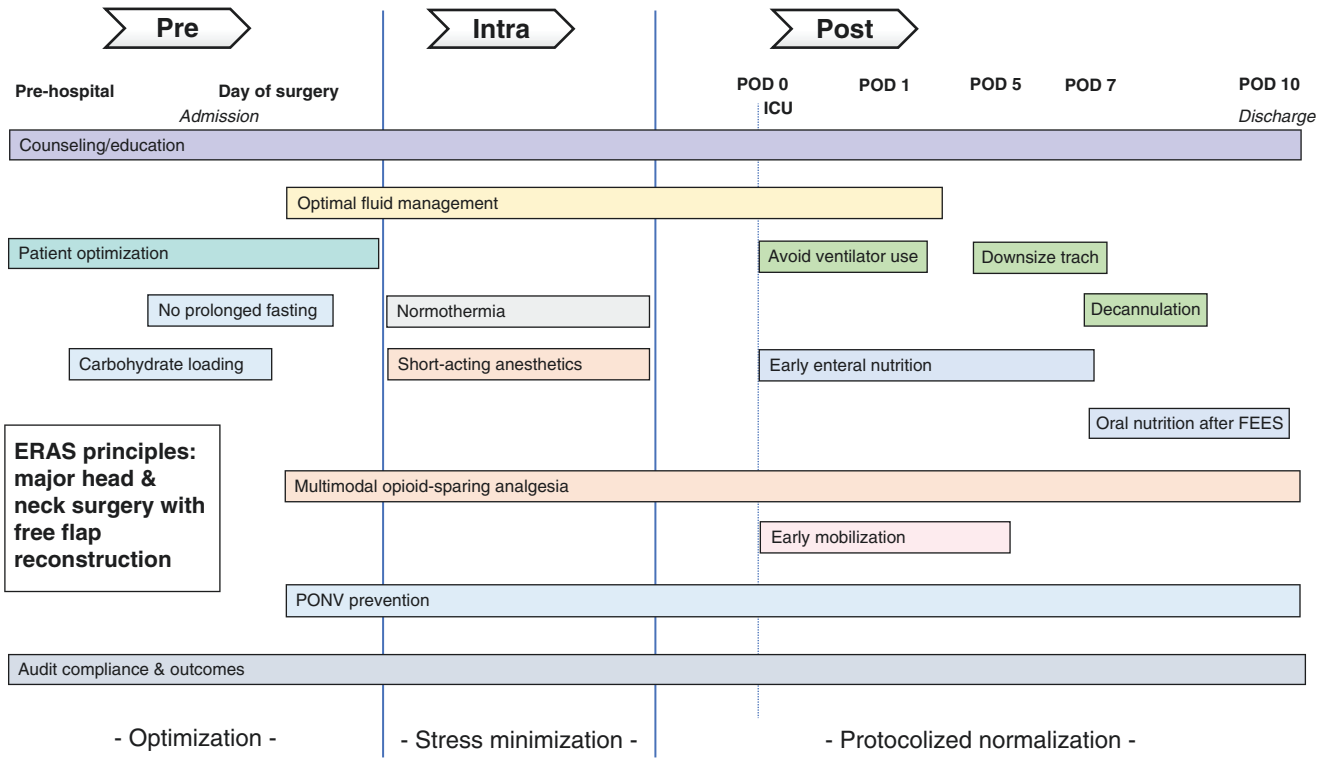

Fig. 50.2 ERAS for major head and neck surgery with free flap reconstruction. *ICU* intensive care unit, *Trach* tracheotomy, *FEES* fiber-optic endoscopic evaluation of swallowing, *PONV* postoperative nausea and vomiting

Knowledge Gaps

The current literature provides compelling evidence for several of the recommended ERAS interventions. Kehlet's 2002 review article summarizes the evidence and rationale for avoidance of nasogastric intubation, intraoperative normothermia, pain control, antibiotic prophylaxis, and management of postoperative nausea and vomiting (PONV) [29]. Several more recent studies provide the physiologic and pathologic basis for the commonly employed ERAS interventions [31, 32].

However, little is known about the impact of ERAS in patients undergoing major head and neck resection with free flap reconstruction. In particular, care elements such as tracheotomy management, swallowing rehabilitation, wound and flap care, and management of pain and PONV all need to be carefully studied in the head and neck surgery population. Preoperative optimization in head and neck patients is also

Table 50.2 Overall and item-specific compliance for several ERAS measures

	6.1. Hospital compliance measure	6.2. Compliance	
		Baseline	Post-ERAS
Overall compliance		39.9%	60.5%
Preoperative	*Total*	52.9%	86.6%
Preop	Preadmission patient education	0.0%	79.4%
Preop	Preoperative oral carbohydrate treatment	0.0%	76.5%
Preop	Thrombosis prophylaxis	96.0%	94.1%
Preop	Antibiotic prophylaxis before incision	96.0%	97.1%
Preop	PONV prophylaxis administered	72.7%	85.7%
Intraoperative	*Total*	45.3%	48.0%
Intraop	No long-acting systemic opioids given	34.0%	47.1%
Intraop	Forced-air heating cover used	100.0%	97.1%
Intraop	Fluid administration guidance	2.0%	0.0%
Postoperative	*Total*	35.6%	55.6%
Postop	Time to termination of urinary drainage	62.0%	76.5%
Postop	Enteral/nasogastric supplements initiated within the first 24 hours postoperatively	75.0%	87.5%
Postop	Suture closure of tracheostomy site	40.9%	80.0%
Postop	Flap care monitoring every 1 hour for the first 24 hours postoperatively	26.5%	88.2%
Postop	Flap monitoring completed POD2	81.6%	93.9%
Postop	Flap monitoring completed POD3	79.6%	97.0%
Postop	Weight change on POD 1	4.0%	18.2%
Postop	Total IV volume of fluids day 0	34.0%	50.0%
Postop	Pulmonary physical therapy initiated	68.0%	85.3%
Postop	Mobilization at all on day of surgery	6.0%	0.0%
Postop	Mobilization at all on POD1	52.0%	90.9%
Postop	Mobilization on postoperative day 2	0.0%	54.5%
Postop	Mobilization on postoperative day 3	0.0%	51.5%
Postop	30-day follow-up performed	89.8%	97.1%

PONV postoperative nausea and vomiting, *IV* intravenous

an area that requires further exploration. Typical surgical wait times for head and neck patients are shorter than for many other cancers: usual wait times are 2–4 weeks. Therefore, designing and implementing a prehabilitation program that fits into this time frame and offers benefit to patients is a major research question. We believe that by adopting ERAS in the head and neck population, it will be possible to answer these questions in a rigorous, evidence-based manner and to develop better approaches to managing this challenging group of patients.

Organizational Context and Support

Designing an ERAS protocol is something well within the grasp of a cohesive multidisciplinary team. Reviewing the literature, convening meetings and focus groups, and designing care pathways are important steps in starting an ERAS program for any area of surgery including head and neck. However, designing a protocol and implementing it are fundamentally different activities. Implementation requires a committed clinical team as well as an organizational environment that values quality management and supports it with appropriate resources. Resources include support for ongoing measurement, audit, and feedback that extend beyond the initial startup phase and continue into ongoing clinical operations. Lack of ongoing institutional support is a key contributor to failure of ERAS and other care pathway initiatives.

Brent James and colleagues eloquently describe the transition undertaken by Intermountain Healthcare as it moved to become one of the best healthcare systems in the world [9]. Highly functioning microsystems combined with an engaged and supportive mesosystem are necessary components that lead to successful implementation and continuous outcomes improvement. The ERAS® Society runs ERAS Implementation Programs employing breakthrough methodology adapted for driving changes in perioperative care in many countries around the world (www.erassociety.org).

In Alberta, Canada, ERAS was first introduced in 2013 in collaboration with the ERAS® Society for colorectal surgery and has since expanded to numerous other surgical specialties including head and neck. Support for ERAS, including ongoing measurement, audit, and feedback, is provided at a provincial level, and this sustained organizational support has provided significant return on investment. Thanh et al.

showed that in Alberta, every dollar invested in ERAS yielded $4 in savings to the healthcare system [36]. Furthermore clinical outcomes were significantly improved. ERAS would not be feasible without this organizational support.

A subsequent Alberta study highlights some important issues that arise when implementing ERAS in a "real-world" setting across a large health system [37]. In this large retrospective cohort study, the authors found that ERAS was associated with reduced hospital LOS, but the decrease was probably due to a temporal trend and not implementation of ERAS. ERAS was not associated with any harmful outcomes, and there were nonsignificant associations between ERAS and reduced post-discharge mortality, hospital readmissions, and emergency department visits. This apparent lack of effect of ERAS was perhaps due to compliance with care elements of 60% when it is believed that compliance of 70% or greater is most likely to yield optimal outcomes. Nevertheless, this research highlights the importance of conducting studies in real-world settings as a means of augmenting what is learned from randomized controlled trials (RCTs). Translating ERAS from single hospitals to health systems is therefore challenging and requires system-level focus on maintaining compliance across multiple sites.

ERAS in Other Areas of Otolaryngology

Long-term experience with care pathways and more recent experience with a full ERAS implementation at FMC clearly show that better organization and delivery of care combined with robust measurement, audit, and feedback is beneficial for patients undergoing major head and neck surgery with free flap reconstruction. It is also apparent that the "ERAS mindset" among team members transfers to other patients' groups managed on the ORL inpatient service. A laryngectomy clinical pathway that borrows many of the ERAS principles and applies them to this patient group was recently implemented, and there are other areas of otolaryngology care that could benefit from the ERAS approach.

ORL as a specialty is concentrated on same-day or outpatient surgical procedures. Furthermore, designing and implementing ERAS protocols is time-consuming and can be costly. In its current form, ERAS is designed to support the management of patients undergoing inpatient surgery. Although ERAS offers many benefits, it is unlikely it could be applied to all areas of surgical endeavor. A measured approach focusing ERAS on high-cost and/or high-harm procedures is probably the best way to start designing and implementing these protocols.

The question of whether same-day or outpatient surgical procedures/patients could benefit from ERAS is interesting and has not been rigorously studied. High-volume otolaryngology procedures, such as tonsillectomy and endoscopic sinus surgery, as well as evolving procedures, such as transoral surgery, are all worthy of further investigation. Adapting and modifying ERAS principles to these areas of ORL makes sense and is an important area for future research.

Conclusion

ERAS and care pathways and fast-track protocols are well-known and validated tools to improve the quality, safety, and effectiveness of surgical care. These approaches, at least in higher-intensity surgical procedures, represent a standard of care that all high-performing centers should strive to implement. Emerging evidence from large health system ERAS implementations suggests that system-level improvements are challenging to measure. A disciplined focus on measurement, audit, and feedback as well as ensuring compliance are key steps toward sustained improvement. Broader application of ERAS principles to other areas of ORL needs further investigation and represents an important area for future clinical research.

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Cardiac Surgery ERAS

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Introduction

Cardiac surgery has a rich history of outcomes-based implementation of multimodal intervention bundles. In the 1990s, in an effort to limit intensive care unit (ICU) length of stay, a balanced anesthetic technique with reduced opioid dependency anchored the "fast-track" movement in cardiac surgery. Pioneered by Dr. Richard Engelman, the first published fast-track protocol recommended a bundle consisting of patient education, multi-target chemical prophylaxis, early extubation and mobilization, as well as short- and medium-term follow-up [1]. Following implementation of this protocol, extubation times were reduced by 30%, while ICU and hospital lengths of stay were each reduced by 20%. Following widespread adoption, fast-track care strategies have consistently been shown to reduce intubation times and ICU lengths of stay without any adverse increase in mortality or morbidity [2, 3].

Beyond "fast-track," the cardiac surgical community has historically undertaken initiatives that, although not labelled as "enhanced recovery," were focused on optimizing patient care. Examples include designing risk stratification models [4–7], building large multinational databases [8, 9], pioneering new surgical techniques [10], embracing new technologies, and pursuing consensus through a variety of multidisciplinary practice guidelines [11–14]. Progress has been made in developing standardized pathways within the formal ERAS framework. This multidisciplinary and collaborative effort has resulted in the publication of ERAS® Cardiac Society (www.erascardiac.org) evidence-based recommendations for patients undergoing cardiac surgery (Table 51.1) [15].

Unique Challenges

There are unique challenges faced by the cardiac surgical subspecialty in designing and implementing an ERAS program. The result is an enhanced recovery paradox: The very reasons that cardiac surgical patients are likely to benefit from the standardized application of ERAS protocols are often the same reasons that the implementation of such protocols can be difficult to achieve.

Variable Surgical Procedures

Cardiac surgery involves a variety of subcategorizations spanning a wide range of surgical technique and perioperative considerations (Table 51.2). The challenges creating a "one-size-fits-all" enhanced recovery strategy are clear. The use of tailored ERAS protocols in colorectal, pancreatic, and hepatobiliary surgical specialties has been well established [16–18]. A similar subdivision within cardiac surgery is likely necessary in the future for any protocol to be both inclusive and comprehensive.

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Table 51.1 ERAS Cardiac Society recommendations

ERAS component	Recommendation	Level	Grade
Blood conservation	Tranexamic acid or epsilon-aminocaproic acid is recommended during on-pump cardiac surgical procedures	High	Strong
Medical optimization	Perioperative glycemic control is recommended	Moderate	Moderate
Antimicrobial prophylaxis	A care bundle of evidence-based best practices is recommended to reduce surgical site infections	Moderate	Moderate
Maintaining fluid balance	Goal-directed fluid therapy is recommended to reduce postoperative complications	Moderate	Moderate
Multimodal opioid-sparing analgesia	A multimodal, opioid-sparing, pain management plan is recommended postoperatively	Moderate	Moderate
Control of body temperature	Persistent hypothermia after cardiopulmonary bypass should be avoided in the early postoperative period	Moderate	Moderate
Tube and drain management	Maintenance of chest tube patency is recommended to prevent retained blood	Moderate	Moderate
Postoperative optimization	Postoperative systematic delirium screening is recommended at least once per nursing shift	Moderate	Moderate
Pre-admission optimization	Smoking and hazardous alcohol consumption should be stopped 4 weeks before elective surgery	Low	Moderate
Postoperative optimization	Early detection of kidney stress and interventions to avoid acute kidney injury are recommended following surgery	Moderate	Moderate
Postoperative optimization	Rigid sternal fixation can be useful to improve/accelerate sternal healing and reduce mediastinal wound complications	Moderate	Moderate
Pre-admission optimization	Prehabilitation is recommended for patients undergoing elective surgery with multiple comorbidities or significant deconditioning	Moderate	Moderate
Medical optimization	An insulin infusion is recommended to treat hyperglycemia in all patients postoperatively	Moderate	Moderate
Postoperative optimization	Strategies to ensure extubation within 6 hours of surgery are recommended	Moderate	Moderate
Patient engagement	Patient engagement tools, including online/application-based systems to promote education, compliance, and patient-reported outcomes, are recommended	Low	Moderate
Prophylaxis against thrombosis	Chemical thromboprophylaxis is recommended following surgery	Low	Moderate
Pre-admission optimization	Preoperative measurement of hemoglobin A1c is recommended to assist with risk stratification	Low	Moderate
Pre-admission optimization	Preoperative correction of nutritional deficiency is recommended when feasible	Low	Moderate
Preoperative optimization	Clear liquids may be continued up until 2–4 hours before general anesthesia	Low	Weak
Preoperative optimization	Preoperative carbohydrate loading may be considered before surgery	Low	Weak
Tube and drain management	Stripping or breaking the sterile field of chest tubes to remove clot is not recommended	High	No benefit
Control of body temperature	Hyperthermia (>37.9 °C) while rewarming on cardiopulmonary bypass is potentially harmful and should be avoided	Moderate	Harm

Table 51.2 Examples of a variety of surgical techniques that could be categorized as "cardiac surgery" from an ERAS perspective

Coronary	Valve	Aortic	Percutaneous	Heart Failure	Other
Coronary bypass CABG + valve Off-pump CABG Robot-assisted CABG Coronary artery unroofing	Single valve replacement Single valve repair Multiple valve procedures Minimal incision valve surgery	Aortic root Ascending aorta Aortic arch Descending thoracic aorta Thoracoabdominal aorta Hybrid repairs (open + TEVAR)	TAVI/TAVR MitraClip Valve-in-valve implantation procedure ASD repair LA appendage occlusion Pulmonary vein ablation TEVAR	LVAD RVAD Biventricular assist device Total artificial heart Heart transplant	Arrhythmia surgery (Cox-Maze, Convergent) ASD repair VSD repair Anomalous pulmonary vein repair Other pediatric and adult congenital

Abbreviations: *ASD* atrial-septal defect, *CABG* coronary artery bypass graft, *LA* left atrium, *LVAD* left ventricular assist device, *RVAD* right ventricular assist device, *TAVI* transcatheter aortic valve implantation, *TAVR* transcatheter aortic valve replacement, *TEVAR* thoracic endovascular aortic repair, *VSD* ventricular-septal defect

Increased Patient Perioperative Multimorbidity

The increasing burden of perioperative morbidities in older patients undergoing cardiac surgery poses several challenges, many of them unique to the specialty. Cardiac disease seldom exists in isolation and typically coexists with multiple multi-system comorbidities (Table 51.3). These conditions increase the perioperative risk for mortality and both short- and longer-term morbidity, making them important targets for ERAS protocols. They also add to the challenge of designing a protocol that will accommodate the wide variety of diseases, their effects on multiple organ systems, and their impact on the postoperative recovery phase.

Table 51.3 Potential patient comorbidities in cardiac surgical patients

Vascular disease
Hypertension
Cerebrovascular disease
Peripheral vascular disease
Venous insufficiency
Pulmonary disease
Congestive heart failure
COPD
Interstitial lung disease
OSA
Pulmonary hypertension
Renal dysfunction
Cardiorenal syndrome
Diabetic nephropathy
Hypertensive nephropathy
Acute kidney injury
Endocrine/metabolic
Diabetes mellitus
Dyslipidemia
Osteoporosis
Hematologic
Anemia
Bleeding diathesis
Thrombophilia
Antiplatelet medications
Anticoagulant medications
Thrombocytopenia
Rheumatologic
SLE
RA
Ankylosing spondylitis
Immunosuppression
Neoplastic
Cardiac tumors
Carcinoid
Radiation-induced heart disease
Chemotherapy-induced heart disease
Infectious
Endocarditis
Rheumatic heart disease
Genetic
Congenital heart disease
Hereditary aortopathies
Connective tissue disorders
Hepatic dysfunction
Cirrhosis
Congestive hepatopathy

Abbreviations: *COPD* chronic obstructive pulmonary disease, *OSA* obstructive sleep apnea, *RA* rheumatoid arthritis, *SLE* systemic lupus erythematosus

Cardiopulmonary Bypass

Cardiopulmonary bypass (CPB) is unique to cardiac surgery and represents both a target and a challenge for an ERAS program. The use of CPB activates many inflammatory, sympathetic, immune, humoral, and coagulation pathways (Fig. 51.1). Systemic inflammatory response syndrome (SIRS) is nearly universally seen following the use of CPB [19–22]. Sympathetic nervous system activation, a priority target for many ERAS protocols, is also highly prevalent [23]. Moreover, the cardiac surgical patient is often systemically cooled, and some operations, including those of the aortic arch, utilize deep hypothermia and even planned circulatory arrest. The need for CPB and cooling/rewarming introduces additional considerations regarding anticoagulation, temperature management, coagulation monitoring and transfusion, goal-directed therapies, advanced monitoring, and organ protection.

Broad Spectrum of Multidisciplinary Care

It is common for cardiac surgical patients to begin their postoperative recovery in an intensive care unit. This provides patients with access to continuous advanced monitoring, multidisciplinary assessment and management, supportive therapies for multi-organ dysfunction, and focused attention to return to normal function (i.e., mobility, enteral nutrition, physical rehabilitation). The inner workings of a modern postsurgical ICU have many moving parts, typically involving a large interdisciplinary team whose members contribute in different but complimentary ways to the patient's recovery. From an ERAS standpoint, this is beneficial; it provides several perspectives and targets for potential enhanced recovery interventions. However, it also adds complexity when attempting to make a protocol comprehensive enough to extract the potential benefits.

The cardiac surgery patient is at the center of any ERAS program. The importance of incorporating non-physician disciplines such as nursing (operating room, ICU, and ward), perfusionists, respiratory therapists, physiotherapists, dieticians, and pharmacists cannot be understated as they are crucial contributors to optimal delivery of patient care in the post-cardiac surgery patient. Out of necessity, any ERAS program will also require the involvement of a diverse group of physicians in addition to these non-physician individuals: cardiac surgeons,

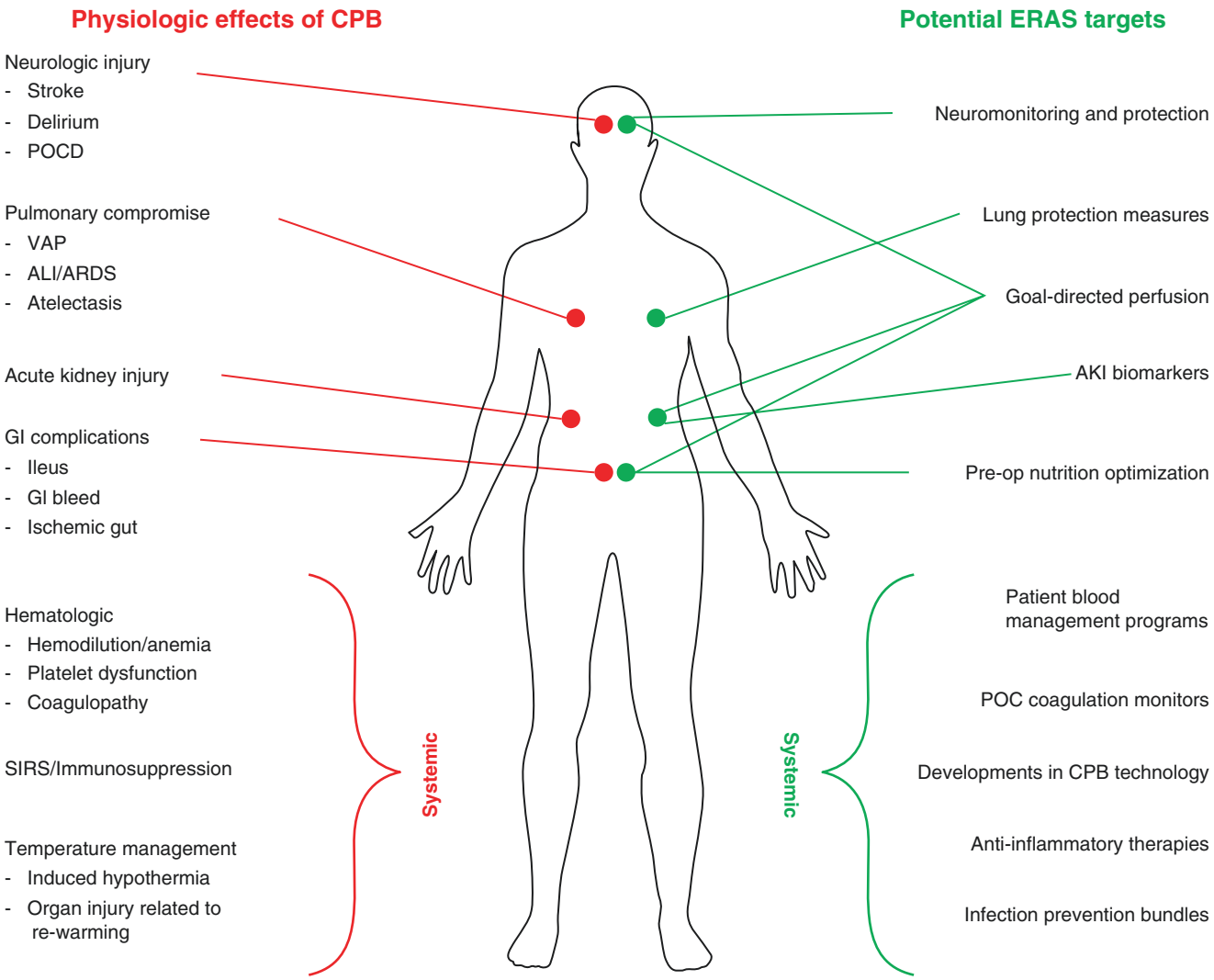

Fig. 51.1 Examples of the potential detrimental physiologic effects of cardiopulmonary bypass (CPB), as well as potential targets to be explored within an ERAS cardiac program. Abbreviations: *AKI* acute kidney injury, *ALI* acute lung injury, *ARDS* acute respiratory distress syndrome, *GI* gastrointestinal, *POC* point-of-care, *POCD* postoperative cognitive dysfunction, *SIRS* systemic inflammatory response syndrome, *VAP* ventilator-associated pneumonia

cardiologists (including various cardiology sub-specialists), cardiac anesthesiologists, intensivists, pulmonologists, endocrinologists, and others. Coordinating all the various stakeholders is an essential albeit challenging endeavor. The team members must be engaged, consulted, and invested in the success of any ERAS program for it to succeed.

Lack of Pre-existing Evidence

ERAS programs are more successfully adopted and implemented when they are based on robust evidence. The initial colorectal ERAS protocol (and subsequent subspecialty protocols) has bundled best-practice interventions based on pre-existing evidence. Many of the common ERAS interventions, such as preoperative carbohydrate loading, multimodal analgesia, antiemetic prophylaxis, peripheral nerve block techniques, intraoperative normothermia, and glycemic control, have either poor or conflicting evidence in the cardiac surgical population [24]. The unique characteristics of cardiac surgical patients and their perioperative care make transference of non-cardiac evidence problematic. Moreover, a large evidence gap exists in many areas that would be considerations for an ERAS protocol, such as CPB mean arterial pressure parameters, ultrafiltration, cooling/rewarming, etc. The current ERAS Cardiac Society recommendations are an important first step (Fig. 51.2), but further research should provide the basis for these additional areas to be incorporated into future guidelines.

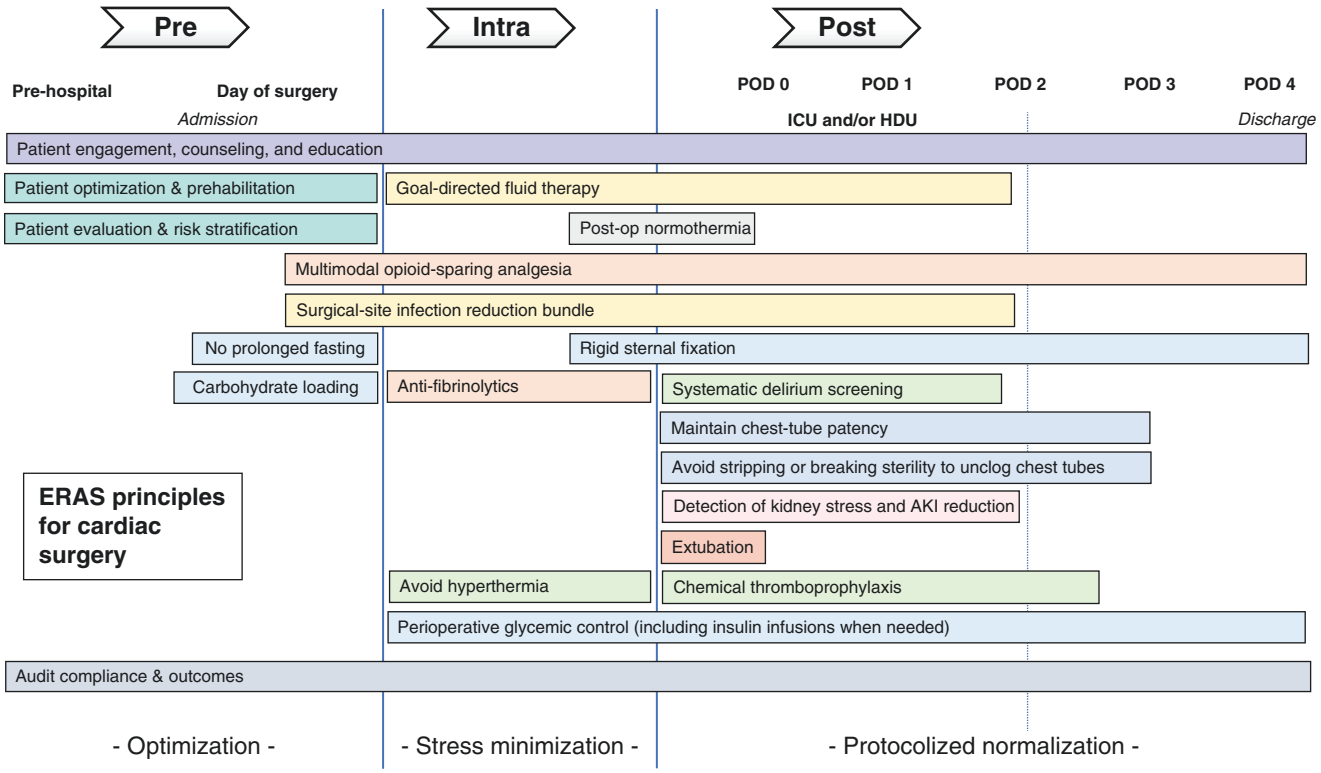

Fig. 51.2 ERAS treatment principles for cardiac surgery. *ICU* intensive care unit, *HDU* high-dependency unit, *AKI* acute kidney injury

Special ERAS Considerations in the Cardiac Surgical Patient: Preoperative

Frailty and Prehabilitation

Prehabilitation (or "prehab") optimizes preoperative functional capacity with the goal of enabling patients' organ systems to better withstand the physiologic stress of surgery [25, 26]. Exercise is a vital component of any prehabilitation program [27–29]. A comprehensive prehabilitation approach to the cardiac surgery patient should also include significant dedication of time and effort toward patient education and psychosocial support. Raising patients' physical and psychological readiness for surgery should help reduce postoperative complications, shorten hospital length of stay, and provide a more seamless transition to recovery following discharge back into the community [25, 30, 31]. One barrier is that cardiac surgical patients are often scheduled emergently or semi-urgently, reducing the window of opportunity to provide prehabilitation. Another is that the degree of cardiac disease may limit the amount of physical activity that can be safely performed, though this issue can often be resolved with appropriate planning and supervision during exercise activities. Finally, though it is generally seen as a low-risk intervention with broad benefits, a robust program would require new inputs of time, labor, and cost. More studies demonstrating a direct relationship between raising preoperative functional capacity and improved perioperative outcomes are needed [32, 33].

Glycemic Control and Insulin Infusions

Management strategies for control of blood glucose are important in each phase of care of the cardiac surgical patient: preoperative, intraoperative, and postoperative [34–36]. Preoperatively, optimal glycemic control, as defined by an HbA1c < 6.5%, has been associated with significant decreases in the incidence of deep sternal wound infection, ischemic events, and other complications [37, 38].

The morbidity of hyperglycemia is likely multifactorial and has been attributed to glucose toxicity, increased oxidative stress, development of a prothrombotic state, and inflammation [39–41]. Insulin infusions may contribute to postoperative hypoglycemia, particularly when a tight blood glucose target range (e.g., 80–110 mg/dl or 4.4–6.1 mmol/l) is selected [39, 42, 43]. Therefore, although perioperative glycemic control with insulin infusions is recommended, more high-quality studies are needed in this area [44].

Special ERAS Considerations in the Cardiac Surgical Patient: Intraoperative

Bleeding, Coagulation, and Transfusion

Perioperative management of the hematologic system and transfusion practices are complex topics, having been previously reviewed in a multi-society publication of comprehensive guidelines [13]. Cardiac surgical patients are among the highest in terms of required transfusion of blood products and are proportionately one of the largest consumers of hospitals' blood supply [45]. Anemia, with reduced oxygen delivery, can result in increased physiologic stress at the cellular level, leading to organ injury and dysfunction [46, 47]. However, increased infection rates, transfusion reactions, organ injury, increased cost, and mortality are all associated with transfusions [48–50]. The Transfusion Requirements in Cardiac Surgery study (TRICS III) demonstrated that a transfusion trigger of 7.5 g/dL was not associated with an increase in 30-day and 6-month mortality, nonfatal myocardial infarction, stroke, or renal failure requiring dialysis compared to transfusing at a trigger of 9.5 g/dL in the operating room (OR) and 8.5 g/dL on the postsurgical ward [51, 52].

Postoperative coagulopathy and platelet dysfunction, often a result of CPB, can be life-threatening and often require transfusion of fresh frozen plasma, cryoprecipitate, platelets, and various factor concentrates. Point-of-care testing (POCT) has emerged as a potential tool to assist clinicians in determining the presence, characteristics, and optimum therapies for complex coagulopathic hemorrhage. A recent trial, using rotational thromboelastometry, demonstrated a decrease in the amount of red cell and platelet transfusion, as well as less major bleeding, by treating specific coagulation abnormalities [53]. Other examples of potential POCT monitors for guiding transfusion include systems that use cartridges, functional platelet assay machines, and sonorheometry—where clot firmness is quantified using sound waves [54–56].

Tranexamic acid and epsilon-aminocaproic acid are antifibrinolytic drugs used to reduce surgical bleeding. Both are synthetic lysine-analogues that reversibly block the lysine binding site of plasminogen, which inhibits the lysis of polymerized fibrin [57, 58]. In cardiac surgery, tranexamic acid has been shown to reduce total units of blood products transfused and reoperation for major hemorrhage or tamponade [59, 60]. Higher dosages have been associated with seizures, and a maximum total dose of 100 mg/kg, especially in patients over 50 years of age, is recommended [58, 59, 61].

Goal-Directed Fluid Therapy

Avoidance of excessive fluid administration is a mainstay of other ERAS programs. The additional complexity from altered myocardial function, the need for cardiopulmonary bypass (including the bypass circuit volume), and the prominent effects of surgical stress on vascular endothelium add to the challenges in determining appropriate fluid management in cardiac surgery [62]. Goal-directed therapy (GDT) can assist in the decision process regarding administration of fluids and inotropic/vasoactive pharmacologic support. It involves the use of multiple monitoring modalities, in combination with our knowledge of cardiovascular physiology and pharmacology, to produce a management plan that aims to optimize delivery of oxygen and nutrients to the body's cells in the most efficient manner [63]. The experience with GDT for cardiac surgery is in its early phases, but outcomes suggest potential benefits [64]. A new area of development is the extension of GDT into the cardiopulmonary bypass period [65]. This includes the use of hemoconcentration, where vacuum-assisted filtration reduces the patient's "water" load and increases the concentration of red blood cells. Excessive hemoconcentration may lead to patients being hypovolemic, relying on excessive use of vasoactive medications, and has been associated with postoperative renal injury [66]. Therefore, GDT for the entire perioperative cardiac surgical period is conceptually attractive, but more studies need to be done to decipher the best physiologic goals, the most helpful monitors to direct our actions, and the proper therapies to achieve enhanced recovery outcomes.

Sternal Closure

Most cardiac surgery procedures are performed through a median sternotomy, with the majority using wire cerclage for closure because of the perceived low rate of sternal wound complications and the low cost of wires [67]. This approach does not fully achieve the principles of rigid fixation applied by other specialties: approximation, compression, and stabilization of the bone [68]. Due to concern about inadequate bone healing, most cardiac surgery patients are recovered under "sternal precautions," which limits their ability to mobilize after surgery [69]. Sternotomy closure with rigid plate fixation has demonstrated improved bone healing, fewer sternal complications, and no additional cost compared with wire cerclage at 6 months after surgery [68, 70]. Patient-reported outcomes (PROs) also showed significantly less pain, better upper extremity function, and improved Short Form Health Survey (SF-36) quality of life scores at multiple time points [71]. Additional research has demonstrated a decrease in mediastinitis and painful sternal nonunion [67, 72].

Temperature Management

Protecting patients from hypothermia and its deleterious effects has demonstrated a reduction in surgical-site infections, major cardiac complications, blood transfusion, and hospital length

of stay in vascular and major abdominal procedures [73–76]. Unfortunately, the picture is not as clear for cardiac surgical patients. Certain procedures, such as surgery on the aortic arch, require therapeutic hypothermia to provide neuroprotection during periods of circulatory arrest. The advent of a variety of neurocirculatory perfusion techniques such as selective antegrade cerebral perfusion (sACP) have allowed for safe surgery with warmer temperatures, but most surgeons still use at least mild hypothermia (defined as 28.1–34 ° C) [77].

Even for procedures where circulation is maintained throughout, it is common for surgeons to allow a patient's temperature to drop to varying degrees of hypothermia. Beyond traditional practice patterns, the paucity of evidence and the contradictory interpretation of the data that does exist are significant barriers to adopting a universal temperature goal for cardiac surgical patients. Two reported studies on the use of normothermia had stark differences in their conclusions. One study showed no increase in risk with maintaining normothermia and less transfusion compared to hypothermia [78]. However, a second study suggested an increase in mortality when patients were maintained at normal temperatures [79]. Neither of these studies were specifically designed to assess the full risk-benefit ratio of normothermia vs. mild hypothermia in non-circulatory arrest procedures. Further study will need to be undertaken prior to any decision on the inclusion of this target in an ERAS program.

Regardless of the temperature during CPB, patients should be rewarmed prior to separation from the circuit. Unfortunately it is common for patients arriving in the ICU after cardiac surgery to be hypothermic [80, 81]. Hypothermia is defined as a core temperature <36 °C persisting 2–5 hours after return from the operating room in the ICU [81, 82]. Even mild hypothermia is associated with multiple physiologic derangements including coagulopathy, increased incidence of wound infection, prolonged hospital stay, and death [80, 83–85]. Hypothermia can be reduced by using forced-air warming blankets, warming irrigation, and intravenous (IV) fluids [86–88].

While there is disagreement on the impact of hypothermia in cardiac surgery, no such debate exists on the harm from hyperthermia [14]. Rewarming the patient on CPB too quickly, at elevated arterial perfusate temperatures, or to a final nasopharyngeal temperature above 37 °C can all result in harm to the patient, particularly neurologic injury [89–91]. Hyperthermia has also been associated with increased rates of mediastinal infection and post-op acute kidney injury [92, 93].

Special ERAS Considerations in the Cardiac Surgical Patient: Postoperative

Biomarkers to Reduce Acute Kidney Injury

Acute kidney injury (AKI) complicates nearly 40% of cardiac surgical procedures, doubling total hospital costs and decreasing survival [94–98]. Importantly, AKI increases long-term mortality independent of other risk factors, even if kidney function has recovered [99]. Current diagnostic criteria for AKI rely on changes in serum creatinine or urine output, which reflect kidney function and underestimate the degree of injury or dysfunction [100]. Hemodilution from cardiopulmonary bypass (CPB), volume resuscitation, and liberal diuretic administration can further diminish the utility of these criteria to diagnose AKI in cardiac surgery patients [101].

Two novel renal biomarkers, insulin-like growth factor-binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases-2 (TIMP-2), are involved in G1 cell cycle arrest, are upregulated in renal stress situations, and can help identify patients at high risk for AKI [102]. Despite the predictive power of preoperative renal function biomarkers, preventing AKI through detection of biomarkers of postoperative kidney stress and initiation of a renal-optimization bundle appears to be the superior strategy [103–105]. Urine levels of TIMP-2 and IGFBP7 are predictive for AKI as early as 1 hour after starting cardiopulmonary bypass [106]. High-risk postoperative cardiac surgical patients with positive urinary biomarkers had reductions in incidence of AKI, length of stay (both ICU and hospital), and costs of care following application of an AKI-prevention bundle. An AKI-prevention bundle would include avoidance of nephrotoxic agents (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, nonsteroidal anti-inflammatory drugs, and radiocontrast), close monitoring of serum creatinine and urine output, avoidance of hyperglycemia, and hemodynamic monitoring with the goal of optimizing volume status and hemodynamic parameters using a goal-directed algorithm [107–109].

Chest Tube Maintenance

Chest tubes, which evacuate shed mediastinal blood, are prone to clogging with clotted blood [110]. The incidence of retained blood in prospective observational studies is 9% after isolated coronary artery bypass grafting (CABG), 20% in a broader population of general cardiac surgery patients, and 51% in patients requiring ventricular assist device implantation [111–113]. When this occurs in the setting of active bleeding, the result can be mechanical compression of the heart or lungs, which may require interventions for tamponade or hemothorax [114, 115]. Even if the volume of retained blood is small, hemolysis and thrombin generation promotes an inflammatory process that can contribute to increases in several postoperative complications: the development of pleural and pericardial effusions, postoperative atrial fibrillation (POAF), bleeding, AKI, time of mechanical ventilation, length of stay, and mortality [111, 112, 114, 116].

Traditional methods to minimize chest tube occlusion and retained blood, such as milking or stripping tubes, have been

shown in meta-analyses to be time-consuming, ineffective, and potentially harmful [117–119]. Breaking the sterile field to open chest tubes at the bedside to suction clot has the potential to increase infections and potentially damage internal structures [120]. Active clearance chest tubes are designed to allow for regular clot disruption without breaking the sterile field, allowing for maintenance of patency without the issues identified above. This approach, when compared to conventional chest tube drainage, prevented chest tube occlusion and reduced retained blood in cardiac surgical patients [113, 121–123]. A reduction in retained blood through this approach has demonstrated less reoperations for bleeding and a lower incidence of POAF [113, 116, 121, 123, 124].

Delirium

Delirium has long been recognized as a neurologic complication following cardiac surgery [125, 126]. In recent years, clinicians have gained a greater appreciation for its role in increased healthcare costs and poor postoperative outcomes, including decreased long-term survival, freedom from hospital readmission, and reduced cognitive and functional recovery [127, 128]. While a clear mechanism has not been elucidated, it is felt that delirium is a marker of an injured or injury-prone brain [127].

Current contemporary reports suggest up to 20% of cardiac surgery patients have postoperative delirium (nearly twice the rate observed in other elective non-cardiac procedures) with a three- to eightfold increased risk if the patient has significant preoperative frailty [129–133]. Identification of preoperative frailty improves risk prediction and provides targets for patient optimization. Three key patient factors have emerged: (1) a baseline vulnerability of the brain in the older adult cardiac patient, with lower psychologic, sociologic, and physiologic reserves; (2) experiencing an acute cardiac stressor (i.e., cardiac surgery); and (3) potential brain injury further compounded by postsurgical stressors that include processes of care [134].

An integral component for the prevention of delirium is the establishment of baseline patient factors that are associated with an increased risk of postoperative delirium. Determination of baseline cognition using the Montreal Cognitive Assessment, Mini-Cog, or the Short Portable Mental Status Questionnaire is a key first step and may provide valuable insight into the patient's cognitive reserve [135–137]. Similarly, testing for frailty, abnormal albumin, anxiety, depression, and pre-procedure pain may also provide important information [132, 133, 138–141].

In the intraoperative and postoperative periods, additional monitoring may assist in optimizing cerebral perfusion and neuroprotective strategies. Intraoperative and postoperative hemodynamic perturbations that result in reduced cerebral blood flow (i.e., brain hypoxia) appear to contribute to subsequent brain dysfunction that results in delirium [142–144]. There are, at present, ongoing investigations on the use of near-infrared spectroscopy (NIRS) and modifications in the depth of anesthesia on the occurrence of postoperative delirium [145–147]. Due to the complexity of the various potential mechanisms that have been proposed, it is unlikely that a single intervention (i.e., one pharmacologic agent or treatment) is likely to impact the rates in the cardiac surgery patient [148]. An optimal balance of analgesia, sedation, anxiety, and delirium management in the ICU may result in reduced pain, decreased anxiety, managed delirium, enhanced quality of sleep, and improved recovery [149].

Early Extubation

Prolonged mechanical ventilation after cardiac surgery is associated with longer hospitalization, higher morbidity, mortality, increased costs [150], ventilator-associated pneumonia, and significant dysphagia appearing after extubation [150, 151]. Overutilization of anesthetic agents administered in the operating room and ICU are associated with prolonged mechanical ventilation [152].

Early extubation (generally considered extubation within 6 hours of arrival in the ICU) can be achieved with time-directed extubation protocols and low-dose opioid general anesthesia. Tracheal extubation within approximately 6 hours is commonly shown in studies to be safe and associated with reduced time in the ICU, length of stay, and decreased use of hospital resources [153–159]. Programmatic transitioning to earlier extubation in low- and moderate-risk cardiac surgical patients appears to also provide a cost-effective improvement in outcomes [160]. In a meta-analysis of more than 30 studies, ICU times and length of stay were reduced; however, no difference in morbidity and mortality could be demonstrated due to disparate study designs and under-powering [161].

Multimodal Analgesia

Optimizing postoperative pain control accelerates normalization of quality of life and functionality that may otherwise persist for weeks after an elective operation [162]. During the period of time when patients are intubated and

nonverbal, alternative pain assessments such as the critical-care pain observation tool (CPOT) and behavioral pain scale (BPS) can assist in detecting and properly treating pain [163–165]. Inadequately treated acute pain can contribute to the development of chronic pain, which can occur in up to 20% of cardiac-surgery patients [166]. As in other ERAS programs, multimodal opioid-sparing analgesic strategies strive to optimize analgesia and reduce medication side effects, though special considerations exist for patients having cardiac surgery.

The cardiac surgery patient may be limited in some analgesic strategies regularly used in their non-cardiac surgery counterparts. Nonsteroidal anti-inflammatories (NSAIDs) have been associated with renal dysfunction and myocardial infarction following cardiac surgery [167, 168]. Epidural or spinal analgesia is well described in the cardiac surgical literature, though used by a minority of anesthesiologists [169]. The purported benefits of thoracic epidurals, including decreased opioid requirements, improved pulmonary function, and lower mortality, have been inconsistently demonstrated [170–172]. Given that the risk of epidural hematoma has been estimated in the 1:1500 to 1:6000 range, many centers are hesitant to include this as a standard component of their analgesic plan [170, 173].

Other known options for multimodal adjuncts have less definitive evidence in the cardiac surgery population [24]. Acetaminophen can reduce opioid consumption, but may be insufficient to completely avoid opioids and their related side effects [174]. Tramadol, gabapentin, and pregabalin have all been shown to decrease opioid consumption as part of a multimodal analgesic strategy in cardiac surgery [175–177]. There is a growing interest in dexmedetomidine, an intravenous alpha-2 agonist with anesthetic and analgesic properties, which has demonstrated earlier extubation, reduced delirium, less acute kidney injury, and decreased 30-day and 1-year mortality [97, 178–180]. Unfortunately, the data for all of these options is scarce within the cardiac surgical literature, and further study will be needed to determine the expected analgesic and opioid-sparing capabilities, impact on outcomes, proper usage and dosing, side effect profile, and cost-effectiveness.

Special ERAS Considerations in the Cardiac Surgical Patient: Audit

Audit of clinical practice is an essential component within any ERAS program. Audit allows teams to establish baseline guideline compliance, length of hospital stay, and complications pre-ERAS implementation. It is well established that improved overall ERAS compliance is associated with reductions in both complications and hospital stay [181]. Following implementation of the ERAS program, efforts can be focused on areas where compliance is low and therefore teams iterate toward improved outcomes [182]. Use of either a tailored database or the ERAS Interactive Audit System (EIAS)—a web-based software tool that allows programs to monitor outcomes and protocol compliance on an ongoing basis—can facilitate protocol refinement. Whatever audit tool is chosen, it must include parameters, outcomes, and workflows that are specific to the cardiac surgical patient.

Future Directions

The design and implementation of an enhanced recovery after cardiac surgery program presents a host of challenges unique to the field. Implementation involves a team with designated champions from the cardiothoracic surgical staff, cardiac anesthesia, intensivist, pharmacy, physical therapy, respiratory therapy, advance practice providers, and nursing. Buy-in from the individual care units (outpatient, OR, ICU, and stepdown) is essential. Future areas that will require development include post-discharge monitoring and management, development of cardiac surgical subspecialty pathways, development and validation of nontraditional metrics, and maximizing the use of database and registry reporting. The cardiac surgical team is under increasing pressure to reduce complications and costs while providing the best-possible patient experience. A well-designed and implemented ERAS cardiac program can assist in achieving the goals. However, it requires the combined efforts of perioperative medical-care providers, hospital system administrators, healthcare financial administrators, and most importantly, the patients themselves (Fig. 51.3).

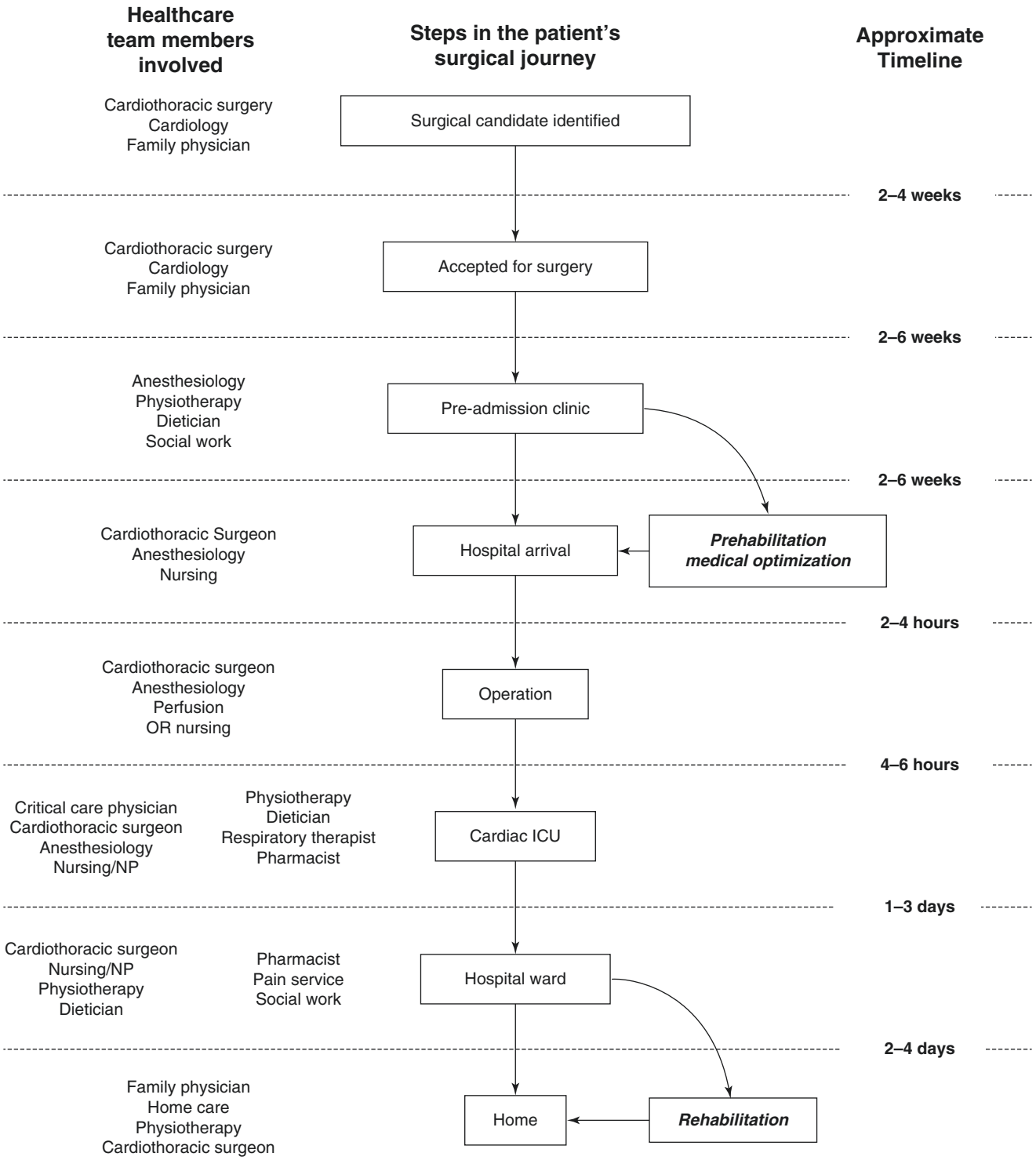

Fig. 51.3 Example of the steps in an elective outpatient's cardiac surgical journey through an ERAS program. A non-exhaustive list of potential healthcare team members who would be contributing to the patient's care, and thus be involved in the ERAS program is provided. In addition, an estimate of the time periods between steps is listed. The actual steps, healthcare team member involvement, and time periods would vary depending on the patient, type of surgery, institution, healthcare system, and scope of the ERAS program. The purpose of the flowchart is to illustrate the multitude of steps, team members, and timeframes that need to be considered when designing and implementing an ERAS program for cardiac surgery. *ICU* intensive care unit

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Vascular Surgery and ERAS

52

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Introduction

As there are multiple different types of vascular operations, with open, endovascular, or hybrid approaches, there are varying complications that can affect the patient's post-procedural course. As operative type and location of incisions vary, so do the specific complications associated with these procedures. Unlike other surgical specialties that tend to perform operations in one area of the body, vascular surgeons perform cervical, upper and lower extremity, transabdominal and retroperitoneal operations. The common thread is the vascular disease with its risk for cerebrovascular and cardiovascular complications. But, in addition, some patients will experience ileus and other commonalities addressed in the hepatobiliary and colorectal guidelines, whereas others will experience difficulty with mobility and have needs similar to patients following orthopedic guidelines. Ideally, vascular teams including surgeons, anesthesiologists, nurses, and therapists have the experience and flexibility to address these challenges with guidance from clinical pathways or protocols. Further engaging patients to participate in preoperative nutrition, tobacco cessation, and exercise programs to help mitigate known risks is also ideal. Unfortunately, the advanced age, frequent comorbidities, decreased mobility, and access to resources of the general vascular patient population can be problematic without clear direction and support from the vascular team. Enhanced recovery after surgery (ERAS), with its emphasis on coordinating and improving perioperative care, may significantly benefit patients undergoing vascular surgery as it has for the patients in many other surgical specialties.

In 2018, the ERAS® Society, ERAS® USA Society, and the Society for Vascular Surgery (SVS) developed a multidisciplinary, multi-society committee to develop ERAS protocols for vascular surgery. The guidelines are being developed in accordance with ECRI Institute regulations. Multiple systematic reviews are being performed by third-party methodologists acting as an honest broker. Through an iterative process, the committee will critically appraise the literature and develop guidelines based on the grading of recommendation assessment, development, and evaluation (GRADE) system [1]. The strength of the recommendations in the GRADE system is based on the quality of the evidence and the risk/benefit ratio of the therapy. In areas where evidence is lacking, no grade will be assigned, but suggested practice based on expert opinion will be provided in order to provide a comprehensive clinical guideline.

Vascular surgery patients have not had the benefit of formalized perioperative care pathways. There is current work being done to synthesize the existing literature describing best practices in the preoperative, intraoperative, and postoperative care of patients undergoing vascular operations. Similar to existing ERAS protocols, the joint guidelines committee from the ERAS societies and SVS will be publishing clinical practice guidelines. Below, the unique challenges and considerations for vascular surgery patients are described.

Aorta

Patients with supra-inguinal atherosclerosis often have many high-risk chronic health problems, such as coronary artery disease, heart failure, diabetes, chronic kidney disease, and cerebrovascular disease, and must often recover from a high-risk, high-stress operation if endovascular options are not

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available. Major complications have been reported to be as high as 20% and 30-day mortality approximately 3.5% [2]. Although the pathophysiology is different from aortoiliac occlusive disease, abdominal aorta aneurysms (AAA) are commonly found in male smokers over the age of 65 years, which is another high-risk surgical population. Treatment options for Abdominal Aortic Aneurysm (AAA) include both open and endovascular approaches, but all are at risk for postoperative complications and hospital readmissions [3, 4].

Although there are no formal guidelines, there are published reports of various ERAS-like clinical care pathways for open abdominal aortic surgery. Based on an exhaustive literature review, 12 articles were identified providing information on ERAS-like clinical care pathways in aortic surgery [5–16]. All of the studies were conducted on patients with either infrarenal AAA disease or aortoiliac occlusive disease. All pathways had similar protocols, including the use of epidural analgesia, oral intake on the day of surgery or postoperative day (POD) 1, and ambulation on postoperative day 1 (Table 52.1 and Fig. 52.1). The studies are limited by study design, heterogeneity, possible confounding, and high risk of bias. However with that caveat, the 12 studies uniformly demonstrated clinically and statistically significant improved outcomes, with patients tolerating regular diets within a median of 3 days of surgery, decreased length of stay to as little as 3 days, and no increase in morbidity and mortality.

The largest reported experience is from the University Hospital of Novara in Novara, Italy [14]. From 2000 to 2014, 1014 patients underwent open aortic surgery as part of a "fast-track protocol." In this case series, 97% of patients tolerated a semisolid diet and 97% walked on the day of surgery. Median inpatient length of stay was only 3 days, and 80% were discharged to their homes by postoperative day 5. Hospitals such as the University Hospital of Novara have shown that it is possible to have dramatically improved results with coordinated clinical care pathways, but their protocol and results may not be generalizable to all aortic surgery populations. More research and clinical quality improvement programs are needed. Special considerations for open aortic surgery patients are discussed as follows.

Preoperative Counseling, Risk Assessment, and Optimization

Discussing the intent to use an ERAS pathway in the perioperative period serves as a platform for setting timelines and goals and can be used to set expectations for postoperative mobilization, nutrition, and discharge. Importantly, in

Table 52.1 Sample open aortic operation pathway

	Preoperative	Day of surgery	POD 1	POD 2	POD 3 – discharge
Preoperative optimization	Discuss intent to use ERAS. Assess need for further preoperative workup based on symptoms, history, and exercise tolerance	N/A	N/A	N/A	N/A
Tobacco	Assess current tobacco use. In office tobacco cessation consult if appropriate	Provide supplemental nicotine therapy	Provide supplemental nicotine therapy	Provide supplemental nicotine therapy	Provide supplemental nicotine therapy. Develop discharge plan for continued abstinence from tobacco
Ambulation/ physical activity	Assess current level of activity. Discuss with patient possible effects of baseline activity on postoperative recovery	Physical therapy consult Out of bed to chair	Ambulate at least once	Ambulate at least 3 times daily	Ambulate at least 3 times daily
Pain control	Assess current sources of pain and medications used. Discuss plan to use regional/local analgesia (i.e., epidural catheter)	Epidural placement preoperatively for use intraoperatively and postoperatively. Management per acute pain team	Continue epidural and multimodal pain medications	Continue epidural and multimodal pain medications	Remove epidural. Continue multimodal pain medications. Wean IV breakthrough pain medications as early as possible
Nutrition	Discuss plan for reduced preoperative fasting and early postoperative enteral nutrition	Clear liquid diet until 2 hours before surgery. Resume clear liquid diet postoperatively	Advance to regular diet. Bowel regimen	Continue regular diet, bowel regimen	Continue regular diet, bowel regimen
Early line and drain removal	N/A	NG tube out postoperatively if placed	Foley out	Daily discussion of need for existing lines and drains	Daily discussion of need for existing lines and drains

POD postoperative day, *ERAS* enhanced recovery after surgery, *N/A* not applicable, *IV* intravenous, *NG* nasogastric

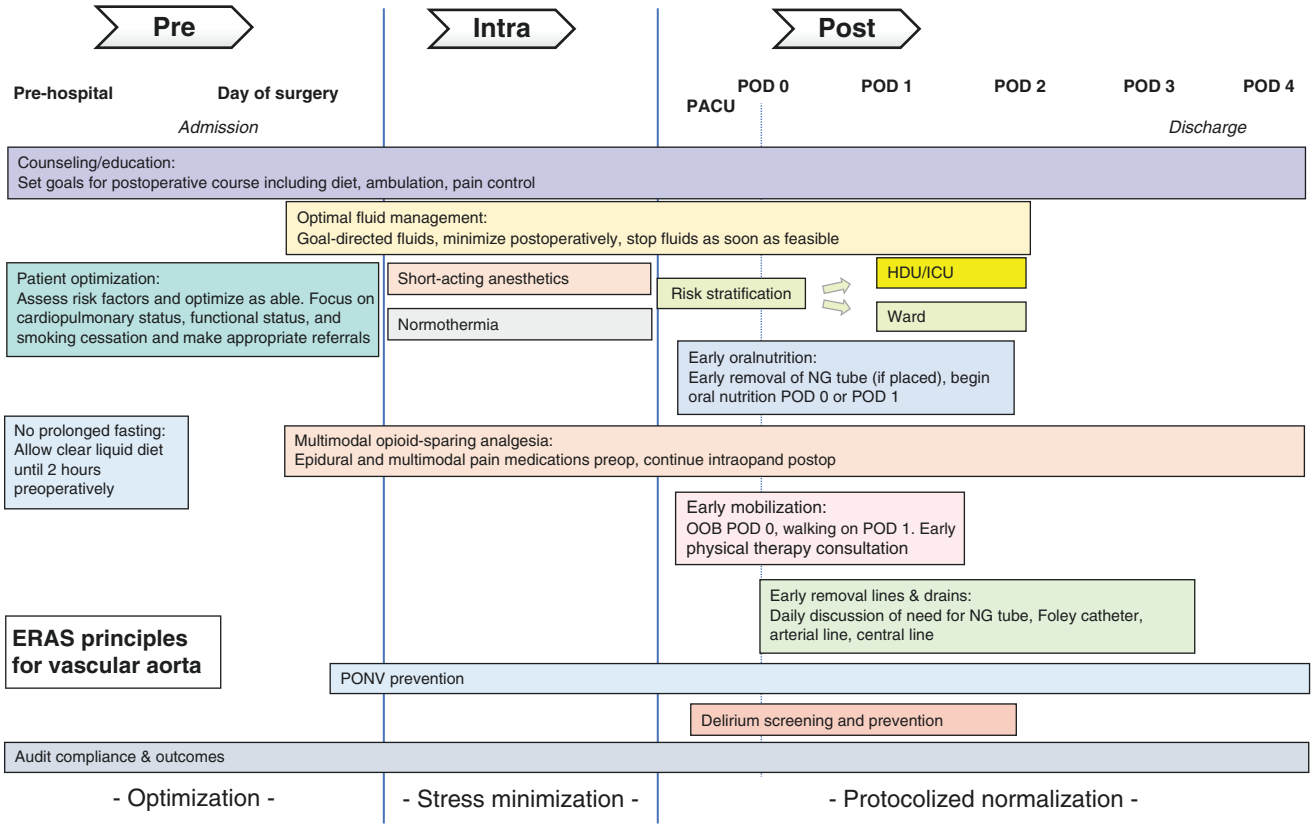

Fig. 52.1 ERAS principles for vascular aorta: Epidural anesthesia, postoperative intake on postoperative day (POD) 0 or POD 1, ambulation POD 1, CLD up to 2 hours before surgery, limited fluids postop (ex, 1 L/day). Preoperative counseling, setting expectations, daily goals, early removal of lines and drains, discharge planning. Medical screening and optimization. Abbreviations: PACU postoperative anesthesia care unit, HDU high-dependency unit, ICU intensive care unit, OOB out of bed, POD postoperative day, NG nasogastric, PONV postoperative nausea and vomiting

vascular surgery, it can also be used to implement a plan for preoperative optimization of chronic medical conditions and lifestyle considerations.

Cardiac Risk Assessment and Optimization

Cardiac disease is one of the most common comorbidities among vascular patients and contributes to increased morbidity and mortality throughout the perioperative period [17]. An ERAS pathway should reinforce the application of preexisting American Heart Association (AHA) guidelines for preoperative cardiovascular optimization. Based on the AHA guidelines, appropriate laboratory tests, electrocardiograms, echocardiograms, and stress testing should be ordered to assist with preoperative cardiovascular risk assessment and management. Beta-blockers, angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs), statins, and antiplatelet agents are part of optimal medical management of vascular disease and should be continued in the perioperative period. Where appropriate, cardiology referral should be placed for assistance with thorough preoperative optimization and also for postoperative management for inpatients at higher than average risk [17].

Anticoagulation

The frequent use of systemic anticoagulation may affect timing of surgery and limit options for regional anesthetic techniques in patients undergoing vascular surgery. Additionally, anticoagulation increases the risk of intraoperative and/or postoperative hemorrhage. This necessitates judicious anticoagulation management strategies. An ERAS pathway could establish a clear preoperative and postoperative plan for anticoagulation cessation and reimplementation. Ideally, this would include guidance regarding preoperative coagulation studies, timing of cessation, and postoperative resumption [18]. Reversal agents for anticoagulants are usually reserved for urgent or emergent indications.

Tobacco Cessation

Tobacco use significantly contributes to the development of vascular disease, increases the risk of perioperative complications, and impairs wound healing postoperatively [19]. The use of tobacco products among patients with vascular disease is estimated to be 70%; thus, incorporating standardized assessment of tobacco usage and providing assistance with tobacco cessation as part of an ERAS pathway would be

particularly beneficial for the vascular population [20]. Patients tend to be motivated to quit during the inpatient stay, and this is an opportune time to encourage efforts to do so. For the patients not ready to abstain from tobacco, pathways should also incorporate a supplemental nicotine treatment regimen (i.e., patches, gum) along with counseling efforts.

Physical Activity

Hayashi et al. found that patients who had regular physical activity prior to open AAA repair had earlier ambulation postoperatively [21]. As might be expected, the earlier ambulation postoperatively was associated with earlier hospital discharge. In this study, regular physical activity was defined as at least 30 minutes of exercise twice weekly for at least 1 year. The exact amount of weekly activity and duration of activity needed to achieve the benefit seen in this study is not known. However, patients can be counseled that beginning or continuing an exercise regimen preoperatively may contribute to a decreased length of stay and accelerated recovery. In addition, knowledge of a patient's baseline level of activity can be taken into account when discussing the expected postsurgical timeline.

Perioperative Pain Control

Regional Analgesia

In the 12 existing publications related to ERAS-like pathways in open aortic surgery, epidural analgesia is consistently incorporated. Studies that have used epidural anesthesia as a component of their ERAS pathway have had promising outcomes, including decreased complication rates, faster time to extubation postoperatively, shorter intensive care unit (ICU) stay, and shorter hospital stay [6, 9, 11–13, 15, 16]. Some of these studies have even reported adequate pain control without the use of any opioids [6, 14, 16]. Because epidural anesthesia is only a single component of ERAS pathways, the degree to which these outcomes can be attributed to the epidurals as opposed to other aspects of the pathway is unknown. However, mechanisms by which epidurals improve outcomes have been shown in studies of other surgical patients and have been speculated for vascular surgery patients. For example, in coronary artery bypass graft (CABG) patients, epidurals have been shown to decrease epinephrine release, possibly decreasing myocardial ischemia (MI) and thereby decreasing morbidity and mortality [12]. This decreased stress response can be presumed to be at least partially responsible for the decreased complication rates seen in vascular surgery patients who receive epidural anesthesia. In aortic surgery in particular, epidural anesthesia combined with general anesthesia has been shown to decrease the need for postoperative mechanical ventilation as compared to general anesthesia alone. Muehling et al. showed that only 5% of patients with an epidural needed mechanical ventilation postoperatively compared with 33% of those in the "traditional" group who received general anesthesia only [11]. This is hypothesized to be due to a decrease in the use of inhaled anesthetics intraoperatively in patients receiving epidural anesthesia.

Another study compared general anesthesia alone to general plus epidural anesthesia in open aortic surgery and showed no difference in length of ICU stay, length of hospital stay, time to oral intake, time to ambulation, morbidity, or mortality [22]. However, as in Muehling's study the patients in this study who received an epidural were extubated significantly faster than those who received general anesthesia alone [11, 22]. A limitation to the generalizability of this study is the now outdated practice of leaving the operating room and transferring the patient to the intensive care unit still sedated and intubated. Additionally, all of these patients had a nasogastric (NG) tube in place until they had a return of bowel sounds. It is possible that lack of aggressive feeding and ambulation protocols inhibited the possible beneficial effects of the epidural. It may be that the effect of the individual components of an ERAS pathways is synergistic and most beneficial when implemented in their entirety. Further research may shed light on this important question.

Delirium Screening

Delirium is a common comorbidity of vascular patients [23]. Delirium is also an underreported complication that results in decreased functional status [24]. Avoidance of the ICU, minimizing opioid use, early ambulation, facilitating physiologic sleep, optimizing day/night cycles, and visual and verbal orientation reminders may reduce the risk of delirium, but similar to the cardiac surgery ERAS guidelines, routine delirium screening and aggressive use of preventive measures are important.

Nutrition Management

Reduced Preoperative Fasting

Many ERAS pathways in other surgical specialties allow patients to have clear liquids, specifically a high-glucose carbohydrate drink, up to 2 hours prior to surgery. There is no demonstrable benefit to this particular intervention on outcomes after aortic surgery. However, reduced preoperative fasting in animal and human studies has been shown to improve patient well-being, decrease the stress response from surgery, decrease insulin resistance postoperatively, and decrease length of stay [25]. With regard to insulin resistance, this phenomenon is seen postoperatively following abdominal operations and leads to decreased uptake of exogenous glucose and increased endogenous glucose pro-

duction (catabolic state). Insulin resistance postoperatively has been independently linked to length of stay [25].

Early Removal of Nasogastric Tubes and Resumption of Postoperative Nutrition

Traditionally, open aortic surgery has been associated with the expectation that patients will develop a postoperative ileus due to the visceral rotation and mobilization of the duodenum required to expose the aorta. Traditional practice is to place a nasogastric tube in the operating room and leave it in place until the patient had return of bowel sounds or flatus. Shifting this perspective has been a central component of the available studies of ERAS protocols in open aortic surgery [5, 7, 10, 13, 15].

The management of nasogastric tubes in ERAS protocols varies. Some centers do not place NG tubes at all, some place them selectively, and some place them routinely and remove them at the end of the case or on the first postoperative day. These studies suggest that postoperative ileus is less common than previously thought. The likelihood of developing an ileus may depend on the surgical approach and whether the bowel is eviscerated. Studies comparing surgical approaches directly have not been performed. Early nutrition has been tolerated in patients undergoing both transperitoneal and retroperitoneal aortic operations. Results have suggested that it is safe to give patients enteral nutrition as early as postoperative day 0 and that early nutrition may improve outcomes.

Promotility Agents

Some studies of ERAS in aortic surgery specifically commented on the use of bowel regimens postoperatively to aid in return bowel function. The most commonly used agent was scheduled metoclopramide. Other agents included misoprostol, vegetable fibers, and senna. There is no clear evidence to recommend for or against the routine use of these medications, but it is reasonable to recommend a bowel regimen as deemed necessary given the bowel manipulation as well as the routine use of opioids. One study implemented a postoperative chewing gum protocol and found that chewing gum 3 times daily was associated with a shorter time to bowel sounds, food intake, and mobilization, though length of stay was not significantly different [26].

Nutrition

Most studies of ERAS protocols in open aortic surgery have offered patients clear liquids about 2 hours postoperatively and a regular diet by late POD 0 or on POD 1, which is considerably sooner than traditional practice. A change in expectation of surgeons of how open aortic surgery patients will progress postoperatively is important. The available literature suggests that patients tolerate an early nutrition regimen and combined with an ERAS protocol, they have better outcomes and earlier discharge without an increase in complications.

Early Postoperative Mobilization

The 12 identified ERAS studies in aortic surgery patients uniformly include early mobilization. Generally this was defined as out of bed to chair on POD 0 and walking on POD 1. Early mobilization is felt to contribute to reduced rates of complications (such as deep vein thrombosis [DVT] and pulmonary complications) and to earlier return of bowel function and possibly earlier discharge. As this is a patient- and nursing-driven effort, implementation of an ERAS protocol should include both patient and nursing education. Other components of the protocol, such as improved pain control with epidural catheters and earlier removal of lines and drains, may help promote early mobilization. As discussed in the preoperative section, patients' baseline physical activity may predict their postoperative mobility, and counseling about activity should begin as early before surgery as possible. This is of particular importance to the vascular surgical population that tends to be older, frailer, and more likely to have preexisting mobility limitations.

Intravenous Fluid Management

Intravenous (IV) fluid management can be a particular challenge in this group of patients, who may have congestive heart failure, chronic kidney disease, or other conditions that mandate precise and goal-directed fluid management. An additional consideration that requires expert management is physiologic changes in cardiac preload and afterload due to aortic cross clamping. Suprarenal clamping also impacts renal perfusion and must be accounted for with the fluid management.

Multiple studies have shown the benefits of goal-directed fluid therapy in many types of operations including vascular procedures. A meta-analysis of 41 randomized controlled trials (RCTs) evaluating perioperative fluid management for different operations found that patients who received goal-directed fluid therapy as opposed to traditional management had significantly lower complication rates and lower postoperative lactate levels. However, the meta-analysis failed to show a significant difference in length of stay or mortality [27].

Two of the RCTs in the meta-analysis evaluated fluid management in patients undergoing open aortic surgery. The first found that patients who were treated with goal-directed therapy had lower complication rates and lower postoperative C-reactive protein (CRP) levels with no difference in other inflammatory markers or length of stay [28]. The second failed to show a difference in complication rate or length of stay [29]. A third RCT not included in the meta-analysis randomized 22 patients undergoing elective open abdominal aneurysm repair to fluid restriction or standard management. The fluid-restricted group had lower complication rates and decreased length of stay [30]. A retrospective review by the

same author found that patients who developed major complications (such as MI, pneumonia, pulmonary edema, or acute renal failure) after open abdominal aortic aneurysm repair were more likely to have received higher volume of fluids and to have a net positive fluid balance compared to patients without complications [31].

Some of the available studies of ERAS in vascular surgery also include a component of postoperative fluid restriction in their protocols. Examples of postoperative fluid management plans include limiting IV fluids to 1 L per day or stopping fluids once the patient was tolerating a clear diet [12, 14]. As with other components of ERAS in vascular surgery, no definitive conclusions on the specific effects of fluid management on outcomes can be reached at this time.

Early Drain and Line Removal

Like other components of ERAS pathways, the effect of the early removal of lines and drains postoperatively has not been studied as a single intervention. Nonetheless, it is not unreasonable to assume that early removal of lines and drains has contributed to the overall benefits of ERAS pathways in open aortic surgery. Early Foley catheter removal should decrease the risk of urinary tract infection risk and increase mobility. In this more elderly population, special attention must be given to early recognition and treatment of urinary retention after Foley catheter removal. Other lines such as central venous catheters and arterial lines were not mentioned in the available literature but should be removed as soon as feasible. Several ERAS pathways transferred postoperative patients to the floor from the recovery unit as long as they were hemodynamically stable. Avoidance of routine ICU admission has many potential benefits including earlier removal of lines as well as potentially reduced delirium, earlier mobilization, shorter hospitalization, and reduced costs.

Lower Extremity

Peripheral arterial disease (PAD) is the most common indication for lower extremity vascular surgery [32, 33]. This patient population is also commonly found to have concurrent heart disease with a higher risk of cardiovascular mortality than those patients with primary coronary artery disease [34–36]. In addition to heart disease, there is a high prevalence of chronic health conditions such as diabetes, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), and renal disease [37]. This patient population is also more likely to suffer from post-procedural delirium [38]. The presence of multiple comorbidities in patients with infrainguinal atherosclerosis leads to a high rate of perioperative morbidity, mortality, and hospital readmissions [38, 39].

There have not yet been studies of the use of ERAS protocols in patients undergoing lower extremity vascular surgery, and more information is needed (Table 52.2). However, pain control and mobility, two common aspects of ERAS pathways, have been studied (Fig. 52.2).

Pain Control

There is an increased prevalence of opioid use among vascular patients for the treatment of chronic pain [40]. Many patients requiring lower extremity vascular surgery have preexisting chronic pain often treated with opioids. The regular use of opioids can have a major impact on analgesic management of patients in the perioperative period.

ERAS pathways for patients undergoing lower extremity revascularization should accommodate the needs of both opioid-naive patients and chronic opioid users. The management pathway for chronic opioid users can be challenging. For these patients, an ERAS pathway should incorporate the degree of opioid usage, and also the reason for opioid use, as an operation may reduce or eliminate the patient's source of chronic pain. For patients who have a direct improvement in their chronic pain from revascularization, the prescribed regimen should include a tapered dosage. Patients with chronic pain unaffected by the operation will most likely require analgesics in addition to their baseline analgesic regimens to adequately control their postoperative pain.

Continuous peripheral nerve blocks (CPNBs) may be particularly useful for patients undergoing lower extremity vascular surgery [41]. In the opioid-naive patient, standardized, multimodal, and opioid-sparing analgesia including CPNB should hasten recovery and reduce the use of analgesics in the perioperative period. In the opioid-tolerant patient, CPNBs have the potential to reduce additional need for opioids in the perioperative period. Although their use has been referenced in the context of ERAS pathways for patients undergoing other lower limb procedures (i.e., knee replacement) [42], there are no reports of CPNB in lower extremity vascular surgery.

Available studies have shown that the use of local analgesia as a central component of pain control regimens in lower extremity vascular surgery is both feasible and beneficial. Licker et al. implemented a local analgesia and sedation protocol for 176 patients undergoing saphenous vein ligation and phlebectomy compared to 200 prior patients who received general anesthesia [43]. Postoperative nausea, dizziness, and headache were reduced to 4% versus 41% ($p < .001$). The mean time to discharge from the ambulatory surgical center was reduced by 364 minutes, allowing the

Table 52.2 Sample lower extremity operation pathway

	Preoperative	Day of surgery	POD 1	POD 2	POD 3 – discharge
Preoperative optimization	Discuss intent to use ERAS. For amputation patients, preoperative OT and PT consult	N/A	N/A	N/A	N/A
Ambulation/ physical activity	For amputation patients, preoperative OT and PT consults for planning of postoperative mobilization and DME	Out of bed to chair or up to side of bed for meals. Amputees to use limb guards for all transfers	Ambulate if possible, continue work with PT and OT. Begin disposition planning	Ambulate twice daily, continue to advance mobility with nurses and therapists. Inpatient rehabilitation assessment if appropriate	Ambulate twice daily, continue to advance mobility. Discharge safety teaching
Pain control	Assess current pain medications used and reasons for use. If chronic pain is expected to improve following revascularization or amputation, plan for postoperative taper of pain medications when appropriate	Multimodal analgesia preoperatively. CPNB catheter placement preoperatively OR liposomal bupivacaine at incisions intraoperatively. Begin IV and PO PRN narcotics	Continue CPNB. Continue multimodal therapy. Continue PRN oral narcotics. Discontinue IV narcotics	Continue CPNB. Continue multimodal therapy. Continue PRN oral narcotics	Remove CPNB. Continue multimodal pain medications. Finalize plan for chronic opioid taper if appropriate
Nursing	N/A	For amputees, assure rigid dressing in place or that soft dressing with limb guard fits properly	Remove Foley catheter	Premedicate by 6 AM for first post-op dressing change	Daily dressing change. Assist with discharge teaching: stump care for amputations, signs and symptoms of infection for all patients

POD postoperative day, *ERAS* enhanced recovery after surgery, *N/A* not applicable, *OT* occupational therapy, *PT* physical therapy, *DME* durable medical equipment, *CPNB* continuous peripheral nerve block, *IV* intravenous, *PRN* as needed

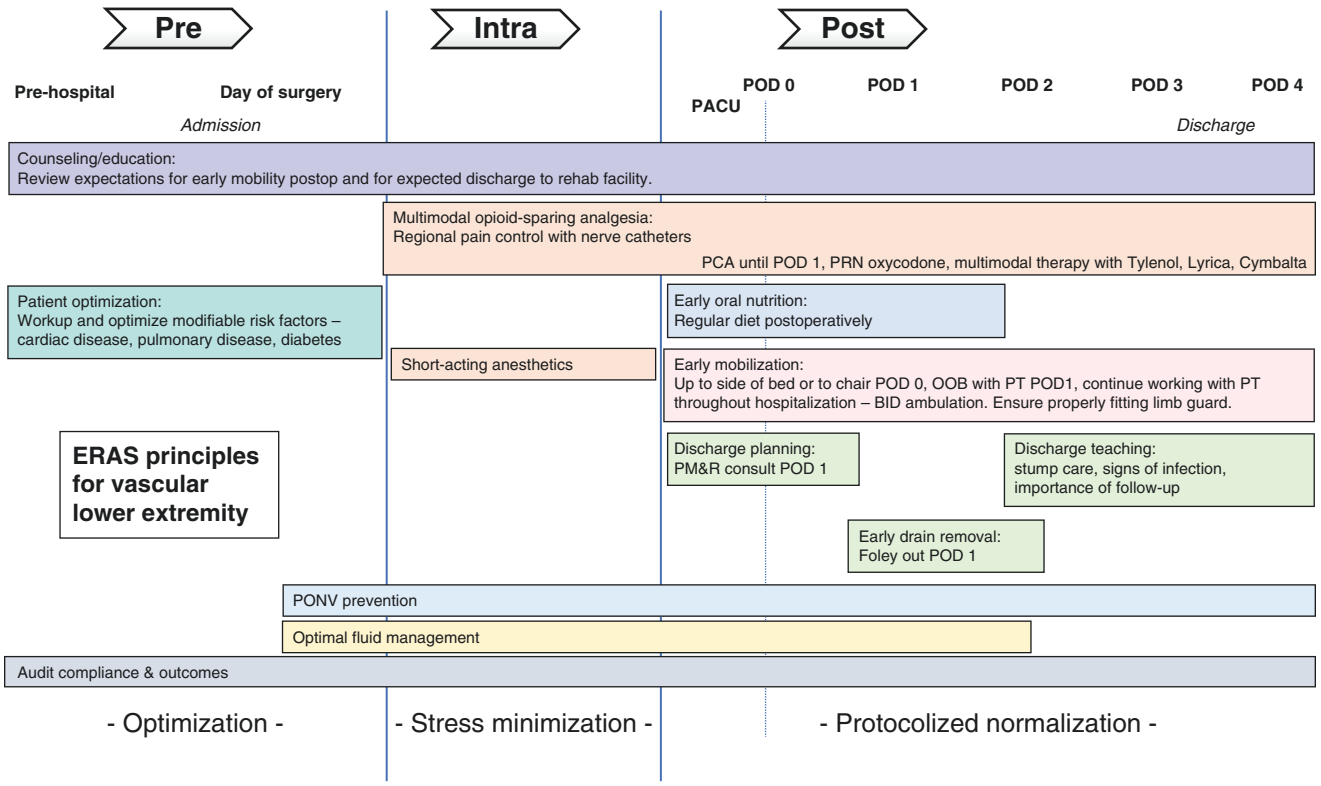

Fig. 52.2 ERAS principles for vascular lower extremity. Abbreviations: PACU postoperative anesthesia care unit, PCA patient-controlled anesthesia, POD postoperative day, OOB out of bed, PT physical therapy, BID twice a day, PM&R physical medicine and rehabilitation, PONV postoperative nausea and vomiting

schedule to accommodate one more case per day without an increase in the rate of complications. Another study showed that above-knee popliteal bypass can be done using local analgesia and sedation with good results [44]. The ten patients in the case series tolerated the procedure well and all ambulated within 8 hours postoperatively.

Mobilization and Prosthetics

Postoperative mobilization is a key component of ERAS pathways. Patients undergoing lower extremity vascular surgery often have preexisting mobility limitations and reduced functional status that may prevent preoperative conditioning. Postoperative mobilization presents unique challenges and may require specific experienced personnel, such as physical therapists. This is a departure from ERAS pathways utilized for other operations including open aortic surgery, where it is realistic to rely on the assistance of nurses or even family members to assist with postoperative ambulation.

For patients undergoing lower extremity amputation, education and expectation management regarding healing, physical therapy, prosthetic fitting, discharge, and rehabilitation is critical. ERAS pathways for amputation patients should incorporate preoperative education, physiatry consult, and ideally a peer visit as well as hands on education dedicated to postoperative limb care [45]. Marzen-Groller et al. created an inpatient protocol for ambulation after amputation [46]. The protocol included a preoperative physical therapy assessment for patients with planned above-knee amputation (AKA), below-knee amputation (BKA), and transmetatarsal amputation (TMA). Therapy plans were initiated preoperatively and continued postoperatively. Postoperative care was team based with both nurses and physical therapists playing key roles. The patients in the study either returned to their baseline mobility scores or even improved. The study also found a trend toward a lower rate of DVT, though this was not statistically significant.

Endovascular

Endovascular procedures are often overlooked when considering ERAS pathways since these minimally invasive procedures are often done on an outpatient basis or only require a short hospital stay. Endovascular interventions are not associated with the postoperative ileus common to intra-abdominal surgery or the pain associated with longer incisions. Although there is not a formal, society-endorsed guideline, the University of North Carolina has published their experience with an ERAS pathway for transcatheter aortic valve replacement [47], which has been shown to reduce the rate of postoperative delirium [48].

There is scant data to guide decisions for patients undergoing catheter-based interventions, but it is reasonable to conclude that ERAS concepts will also benefit these patients. For example, patients undergoing endovascular aneurysm repair are likely to be smokers greater than 65 years old. Preoperative expectation setting and education, smoking cessation counseling, consideration of regional instead of general anesthesia, opioid-sparing multimodal analgesia, goal-directed fluid therapy, and assistance with ambulation after 2–4 hours of postoperative bedrest required after percutaneous arterial access can reasonably be assumed to improve care.

Similar benefit may be anticipated for lower extremity endovascular revascularizations. Pre-procedure education and counseling on a supervised exercise program is beneficial. Additionally, the importance of understanding antiplatelet therapy, smoking cessation, diabetes management, and cardiovascular risk modification in the patients undergoing lower extremity endovascular cases cannot be overstated. With standardized sedation plans and post-procedure care, one could anticipate faster throughput, possibly allowing for increased efficiency and case volume. Reduction in postoperative recovery time and the associated increase in operating capacity has been demonstrated in patients undergoing a “fast-track” venous ligation and phlebectomy in an outpatient surgical center at the University of Geneva in Switzerland. It is reasonable to believe this success can be realized in other settings [43].

Conclusion

ERAS pathways have provided significant benefits to patients, providers, and hospitals when used for many different surgical operations. Although there is a paucity of data for ERAS in vascular surgical patients, we anticipate a similar improvement for our complex, aged, and frail vascular population. There is significant enthusiasm and effort for creating well-designed ERAS pathways for vascular operations. The majority of the existing evidence pertains to open aortic surgery, but there will be utility in ERAS pathways for lower extremity and endovascular surgery as well. Similar to other ERAS pathways, attention to preoperative education, expectation setting, along with modifications in nutrition, mobilization, analgesia, and IV fluid management should result in a better patient experience, improved outcomes, and reduced length of stay.

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Thoracic Surgery

53

Tim J. P. Batchelor

Lung Surgery and ERAS

Lung cancer is the leading cause of cancer deaths worldwide, and, in early-stage disease, surgical resection offers the best chance of cure [1, 2]. However, lung cancer surgery is one of the more traumatic surgical interventions, often causing damage to the nerve, muscle, and bone. It also involves the removal of functional lung tissue. The extent of lung resection is an important factor in determining the risk of postoperative morbidity and mortality and central to all guidelines on determining fitness for surgery.

The combination of surgical trauma and resection of vital functioning tissue, often against a background of deconditioning, chronic obstructive pulmonary disease (COPD), and ischemic heart disease, means that lung cancer surgery is associated with significant complications in up to 50% of cases. This leads to delayed recovery, poorer long-term outcomes, and higher costs [3, 4]. Long-term survival is also reduced, and this effect is more pronounced for more serious complications [3].

Fast-track protocols have been described in thoracic surgery and appear to show an improvement in patient outcomes [5–8]. More recently, specific enhanced recovery after surgery (ERAS) pathways for lung cancer surgery have been published [9–16]. Despite this, the current evidence base for the efficacy of multimodal perioperative care pathways in thoracic surgery lags behind more developed specialties such as colorectal surgery.

Guidelines for ERAS After Lung Surgery

The guidelines for ERAS after lung surgery were commissioned by the ERAS® Society and supported by the European Society for Thoracic Surgery [17]. They document consensus recommendations for the optimal perioperative management of patients undergoing lung resection. The authors were a mix of surgeons and anesthetists who were either experienced in fast-track perioperative care pathways or had specific expertise in certain thoracic-specific elements of an ERAS pathway (e.g., chest drain management). The guidelines were influenced by other ERAS® Society publications, in particular the guidelines on colorectal surgery [18] (see Chap. 40) and gynecological surgery [19] (see Chap. 46).

In some instances, good quality data was not available. Some recommendations had to be based on data extrapolated from other specialties. In other instances, no recommendation could be made due to either equipoise or a paucity of evidence. Individual recommendations were based not only on the quality of the evidence but also on the balance between desirable and undesirable effects. Consequently, strong recommendations were reached from low-quality or conflicting data and vice versa. Some were generic, some were generic but tailored toward thoracic surgery, and others were specific to the specialty (see Table 53.1).

In total, 45 recommendations were developed for enhanced recovery items covering topics related to 4 perioperative phases: preadmission, admission, intraoperative care, and postoperative care (see Table 53.2). The recommendation grade for most of the included ERAS elements was strong, suggesting that the use of a systematic ERAS pathway (Fig. 53.1) has the potential to improve outcomes after thoracic surgery. Since the guidelines are new, there has not been the opportunity to test the package of recommendations presented within. Nevertheless, recent experiences with institution-specific ERAS pathways demonstrate benefits such as reduced opiate usage, minimization of fluid overload, reduced length of stay, decreased hospital costs, and reduced pulmonary and cardiac complications [10–16].

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Table 53.1 Components of the ERAS guidelines for lung surgery detailing recommendations that are generic, recommendations that are generic but tailored toward thoracic surgery, and recommendations that are specific to the specialty

	Generic	Generic/thoracic	Thoracic
Preadmission	Patient education Perioperative nutrition Alcohol dependency management Anemia management	Smoking cessation Prehabilitation	
Admission	Preoperative fasting Carbohydrate treatment Pre-anesthetic medication		
Intraoperative	VTE prophylaxis Antibiotic prophylaxis and skin preparation Preventing hypothermia PONV control	Standard anesthetic protocol	Regional anesthesia Perioperative fluid management Atrial fibrillation prevention Surgical technique: open vs. VATS
Postoperative	Urinary drainage	Early mobilization	Chest drain management

VTE venous thromboembolism, *PONV* postoperative nausea and vomiting, *VATS* video-assisted thoracic surgery

Table 53.2 Guidelines for enhanced recovery after lung surgery: Enhanced Recovery After Surgery (ERAS®) Society and European Society of Thoracic Surgeons (ESTS) recommendations

Recommendation	Evidence level	Grade
Preadmission phase		
Preadmission information, education, and counseling		
Patients should routinely receive dedicated preoperative counseling	Low	Strong
Perioperative nutrition		
Patients should be screened preoperatively for nutritional status and weight loss	High	Strong
Oral nutritional supplements should be given to malnourished patients	Moderate	Strong
Immune-enhancing nutrition may have a role in the malnourished patient postoperatively	Low	Weak
Smoking cessation		
Smoking should be stopped at least 4 weeks before surgery	High	Strong
Alcohol dependency management		
Alcohol consumption (in alcohol abusers) should be avoided for at least 4 weeks before surgery	Moderate	Strong
Anemia management		
Anemia should be identified, investigated, and corrected preoperatively	High	Strong
Pulmonary rehabilitation and prehabilitation		
Prehabilitation should be considered for patients with borderline lung function or exercise capacity	Low	Strong
Admission		
Preoperative fasting and carbohydrate treatment		
Clear fluids should be allowed up until 2 hours before and solids until 6 hours before induction of anesthesia	High	Strong
Oral carbohydrate loading reduces postoperative insulin resistance and should be used routinely	Low	Strong
Pre-anesthetic medication		
Routine administration of sedatives to reduce anxiety preoperatively should be avoided	Moderate	Strong
Intraoperative phase		
Venous thromboembolism prophylaxis		
Patients undergoing major lung resection should be treated with pharmacological and mechanical VTE prophylaxis	Moderate	Strong
Patients at high risk of VTE may be considered for extended prophylaxis with LMWH for up to 4 weeks	Low	Weak
Antibiotic prophylaxis and skin preparation		
Routine intravenous antibiotics should be administered within 60 minutes of, but prior to, the skin incision	High	Strong
Hair clipping is recommended if hair removal is required	High	Strong
Chlorhexidine-alcohol is preferred to povidone-iodine solution for skin preparation	High	Strong
Preventing intraoperative hypothermia		
Maintenance of normothermia with convective active warming devices should be used perioperatively	High	Strong
Continuous measurement of core temperature for efficacy and compliance is recommended	High	Strong

Table 53.2 (continued)

Recommendation	Evidence level	Grade
Standard anesthetic protocol		
Lung protective strategies should be used during one-lung ventilation	Moderate	Strong
A combination of regional and general anesthetic techniques should be used	Low	Strong
Short-acting volatile or intravenous anesthetics, or their combination, are equivalent choices	Low	Strong
Postoperative nausea and vomiting control		
Non-pharmacological measures to decrease the baseline risk of PONV should be used in all patients	High	Strong
A multimodal pharmacological approach for PONV prophylaxis is indicated in patients at moderate or high risk	Moderate	Strong
Regional anesthesia and pain relief		
Regional anesthesia is recommended with the aim of reducing postoperative opioid use. Paravertebral blockade provides equivalent analgesia to epidural anesthesia	High	Strong
A combination of acetaminophen and NSAIDs should be administered regularly to all patients unless contraindications exist	High	Strong
Ketamine should be considered for patients with pre-existing chronic pain	Moderate	Strong
Dexamethasone may be administered to prevent PONV and reduce pain	Low	Strong
Perioperative fluid management		
Very restrictive or liberal fluid regimes should be avoided in favor of euvolemia	Moderate	Strong
Balanced crystalloids are the intravenous fluid of choice and are preferred to 0.9% saline	High	Strong
Intravenous fluids should be discontinued as soon as possible and replaced by oral fluids and diet	Moderate	Strong
Atrial fibrillation prevention		
Patients taking β(beta)-blockers preoperatively should continue them into the postoperative period	High	Strong
Magnesium supplementation may be considered in magnesium deplete patients	Low	Weak
It is reasonable to give preoperative diltiazem or postoperative amiodarone in patients at risk	Moderate	Weak
Surgical technique: thoracotomy		
If a thoracotomy is required, a muscle-sparing technique should be performed	Moderate	Strong
Intercostal muscle- and nerve-sparing techniques are recommended	Moderate	Strong
Re-approximation of the ribs during thoracotomy closure should spare the inferior intercostal nerve	Moderate	Strong
Surgical technique: minimally invasive surgery		
A VATS approach for lung resection is recommended for early-stage lung cancer	High	Strong
Postoperative phase		
Chest drain management		
The routine application of external suction should be avoided	Low	Strong
Digital drainage systems reduce variability in decision-making and should be used	Low	Strong
Chest tubes should be removed even if the daily serous effusion is high volume (up to 450 ml/24 hours)	Moderate	Strong
A single tube should be used instead of two after anatomical lung resection	Moderate	Strong
Urinary drainage		
In patients with normal preoperative renal function, a transurethral catheter should not be routinely placed for the sole purpose of monitoring urine output	Moderate	Strong
It is reasonable to place a transurethral catheter in patients with thoracic epidural anesthesia	Low	Strong
Early mobilization and adjuncts to physiotherapy		
Patients should be mobilized within 24 hours of surgery	Low	Strong
Prophylactic minitracheostomy use may be considered in certain high-risk patients	Low	Weak

VTE venous thromboembolism, *LMWH* low molecular weight heparin, *PONV* postoperative nausea and vomiting, *NSAIDs* non-steroidal anti-inflammatory drugs, *VATS* video-assisted thoracic surgery
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Smoking Cessation

Following lung resection surgery, there is a clear association between smoking and both pulmonary complications and post-operative death [20, 21]. These risks are mitigated slowly by an increasing interval between preoperative cessation and surgery. There is not a clear cutoff point after which surgery is safe.

The evidence that smoking cessation measures actively decrease postoperative morbidity is weak but would appear to be intuitive and is subject to on-going studies. Although no optimal interval for smoking cessation can be identified, patients should be counseled to stop smoking and, ideally, should stop at least 4 weeks before surgery.

Prehabilitation

Only a small proportion of patients with a diagnosis of lung cancer undergo surgical resection. Many present with advanced disease and are therefore not eligible for surgical

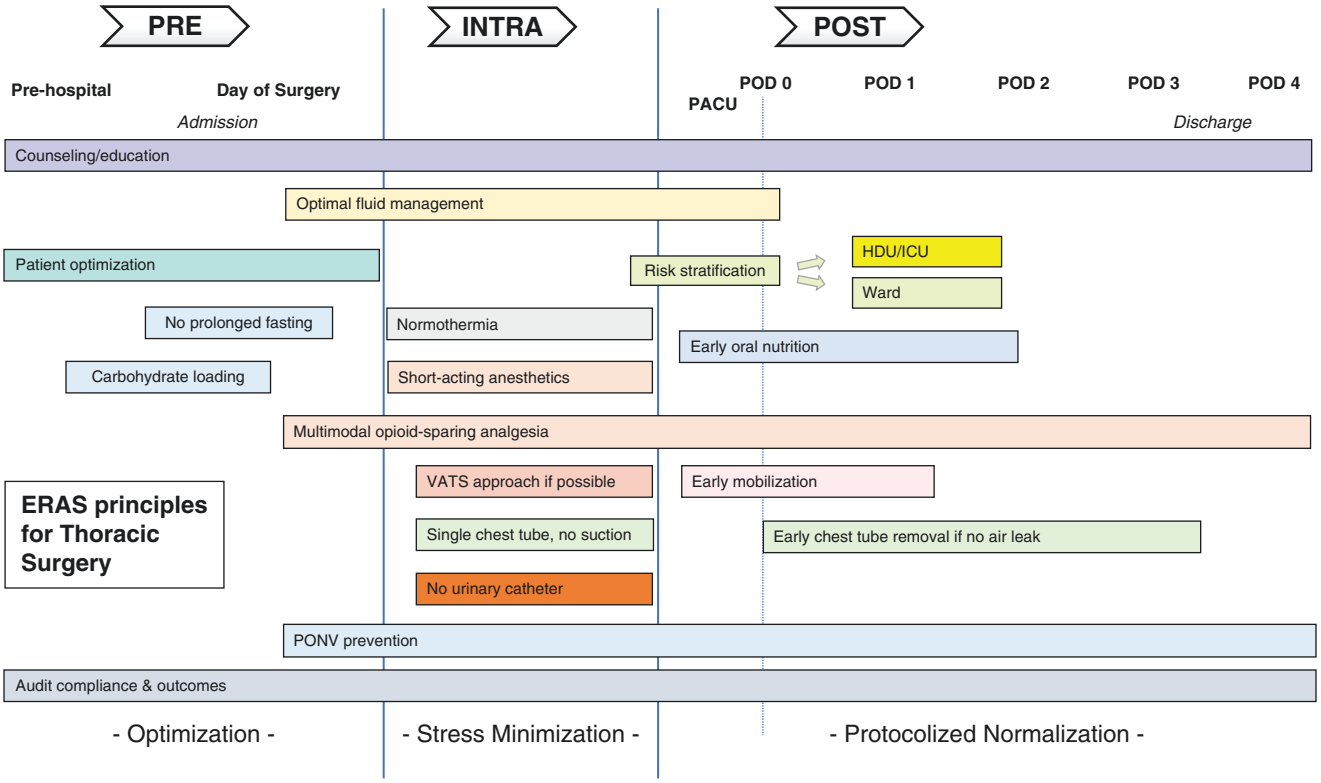

Fig. 53.1 ERAS principles for thoracic surgery. PONV postoperative nausea and vomiting, VATS video-assisted thoracic surgery, HDU high dependency unit, ICU intensive care unit

intervention. Others with early-stage disease may not undergo surgery because of lack of fitness, poor performance status, poor lung function, other comorbidities, or inequity in access to thoracic surgical services.

Addressing the fitness of patients with lung cancer at the time of diagnosis may have two potential benefits. Firstly, those patients previously deemed fit for surgery may have improved outcomes. Secondly, those patients with early-stage disease deemed unfit for surgery may be able to improve their fitness, enabling them to proceed with a lung resection.

Physical inactivity is common in patients with lung cancer. Activity levels appear to be lower than healthy age-matched controls. One explanation is that these patients tend to come from a demographic that have led sedentary lifestyles for a large proportion of their lives. At the same time, fatigue and weight loss as a result of the disease itself can influence a patient's functional status. Poor preoperative exercise capacity is associated with worse long- and short-term clinical outcomes [22, 23]. There is also evidence that it impacts on long-term survival following curative lung cancer surgery [24–26]. This raises an obvious question: Can health outcomes be improved by intervening to improve physical fitness?

Prehabilitation appears to be beneficial before lung cancer surgery [27–30]. There is considerable heterogeneity between studies, and so the exact duration, intensity, structure, and patient selection required to achieve maximum efficacy have yet to be defined. Exercises include aerobic training (lower and/or upper limbs) with the addition of strength training in some studies. Respiratory exercises have also been included in the majority of studies.

Fitness, as measured by peak oxygen consumption (VO_2max), improves significantly in patients with potentially operable lung cancer subjected to pulmonary rehabilitation programs before surgery [31–33]. Medically inoperable patients can become operable over a relatively short 4-week period [32]. Furthermore, preoperative high-intensity training before lobectomy can lead to levels of postoperative fitness comparable to baseline, while those patients who do not exercise may be left significantly impaired [33].

Arguably, it is improvements in postoperative outcomes that are more important than improvements in physiological measures. Hospital length of stay and morbidity were reduced in comparison with standard care in a recent meta-analysis and a Cochrane review [27, 30]. There was also a significant reduction in postoperative pulmonary complications. The effect on pulmonary complications seems to be most important in patients with poor preoperative lung function.

The true role of prehabilitation interventions within an ERAS pathway for lung cancer patients requires further work. The components are yet to be fully defined. In particular, preoperative exercise programs have yet to be standardized in this patient population.

Standard Anesthetic Protocol

One-Lung Ventilation Strategies

No single ventilation strategy during thoracic surgery is favored over another. Practice is influenced by the desire to avoid both hypoxemia and injury to the ventilated lung. The incidence of intraoperative hypoxemia has reduced with time, and so the focus has shifted toward preventing lung injury [34]. One-lung anesthesia with lung-protective strategies may be associated with better outcomes. Decreasing the tidal volumes from traditionally large volumes of 10 ml/kg to 4–6 ml/kg is considered to be more effective in preventing lung injury [35]. However, when smaller tidal volumes are used without positive end-expiratory pressure (PEEP), there is a possible higher incidence of hypoxemia [36]. With the addition of PEEP, oxygenation is equivalent [37]. The optimal level of PEEP will vary according to individual respiratory mechanics and is usually in the range of 5–10 cmH_2O [38].

Attention should also be paid to the non-ventilated operated lung. Avoiding complete collapse of the non-ventilated lung by the addition of continuous positive airway pressure (CPAP) decreases the local intraoperative inflammatory response [39].

Non-intubated Anesthesia

The use of anesthetic techniques that avoid intubation of the airway and positive pressure ventilation has theoretical advantages. These include quicker induction, reduced incidence of lung injury, avoidance of muscle relaxants, and quicker emergence from general anesthesia. The operated lung collapses as soon as the pleura is breached, allowing surgery with near equivalent lung collapse as found during conventional one-lung anesthesia. Potential disadvantages include coughing or movement that interferes with surgery, intraoperative hypoxemia, and an unsafe environment should an intraoperative catastrophe (such as major bleeding) occur.

Non-intubated strategies include awake regional anesthesia and non-intubated general anesthesia with spontaneous ventilation. Regional anesthesia is usually used in combination with intravenous sedation and suppression of the cough reflex (achieved by opiates and intraoperative injection of the vagus nerve [40]). Reported non-intubated thoracic surgical procedures include lobectomy, pneumonectomy, excision of bullae, and lung volume reduction [41]. The majority have been single-center observational studies [42]. Most have shown trends to equivalent or improved outcomes with non-intubated surgery and a trend toward shorter hospital stays [43]. One large randomized controlled trial of patients having a variety of video-assisted thoracoscopic surgery (VATS) procedures showed a decrease in postoperative complications and a shorter postoperative length of stay in the non-intubated epidural group compared to the general anesthesia double-lumen tube group [44]. However, by fast-track standards the hospital stays were very long in both groups, reducing the impact of the results. Consequently, although the technique shows potential, the routine use of non-intubated anesthesia cannot yet be recommended.

Anesthetic Technique

Anesthetic management should focus on short-acting agents that permit early extubation using a combination of regional and general anesthetic techniques. There is an ongoing debate as to whether the use of volatile agents or total intravenous anesthesia (TIVA) with propofol is more advantageous. Modern volatile anesthetics (isoflurane, sevoflurane, and desflurane) are only weak inhibitors of hypoxic pulmonary vasoconstriction, and there is not a clinically relevant higher incidence of hypoxemia when compared to TIVA [45]. However, there are differences with respect to the local inflammatory response in the lungs. Desflurane significantly mitigates the increase in inflammatory markers during surgery in the ventilated lung compared to TIVA [46]. Similarly, sevoflurane decreases the inflammatory response in the non-ventilated lung [47]. While volatile anesthetics appear to decrease postoperative mortality and respiratory complications in cardiac surgery [48], this has not been shown to be true in thoracic surgery [49]. Interestingly, there is an association with improved long-term cancer survival if TIVA is used [50].

Ultimately, the choice of anesthetic agent currently lies with the individual team. Short-acting volatile or intravenous anesthetics are equivalent choices with each having their own merits and disadvantages.

Regional Anesthesia

An ERAS pathway for thoracic surgery must combine multimodal enteral and parenteral analgesia with regional analgesia or local anesthetic techniques while attempting to avoid opioids and their side effects. Postoperative pain is often severe and can be due to peripheral nerve damage, muscle injury, or fractured ribs. However, intercostal nerve injury appears to be the most important factor in its pathogenesis [51]. Indwelling chest tubes may cause ongoing irritation of the pleura and intercostal bundles.

Both thoracotomy and VATS approaches are painful. Although VATS may offer some advantages in terms of pain and quality of life, the effect is relatively modest [52]. Inadequate provision of analgesia exacerbates a compromised respiratory status. Splinting may result in respiratory failure, while an ineffective cough and poor clearance of secretions may lead to pneumonia. Pain increases the immediate risks of hypoxemia, hypercarbia, increased myocardial work, arrhythmias, and ischemia. High-intensity postoperative pain can also facilitate the development of post-thoracotomy pain syndrome.

Preemptive Analgesia

In theory, the provision of preemptive analgesia is attractive. The aim is to decrease acute postoperative pain, even after the analgesic effects of the preemptive drugs have worn off, and to inhibit the development of chronic postoperative pain. Unfortunately, there is little evidence to support this approach in thoracic surgery. Specifically, there is no evidence of benefit for the preemptive administration of systemic opioids, non-steroidal anti-inflammatory drugs (NSAIDs), or ketamine [53]. Preemptive thoracic epidural analgesia (TEA) is associated with a reduction in acute pain after thoracotomy but has no effect on the development of chronic post-thoracotomy pain [54].

Intraoperative Regional Analgesia

TEA has been the gold standard technique for pain control after major thoracic surgery for some time. Initial ERAS protocols in other specialties defined epidural analgesia as the cornerstone of pain management. However, the risks associated with TEA are becoming clearer and may be greater than previously thought [55]. Adverse effects include urinary retention, hypotension, and muscular weakness.

Paravertebral analgesia provides a unilateral block of somatic and sympathetic nerves that lie in the paravertebral space and is particularly useful in unilateral thoracic procedures. Several randomized studies have compared TEA with paravertebral blockade. The results suggest that paravertebral blocks are more effective at reducing respiratory complications than TEA and after the first few hours provide equivalent analgesia [56–58]. Furthermore, the risks of developing minor complications such as postoperative nausea and vomiting (PONV), pruritus, hypotension, and urinary retention are less. Neither technique is inferior to the other in terms of acute pain, 30-day mortality, major cardiorespiratory complications, or length of hospital stay [58, 59].

Intercostal catheters may be as effective as TEA. They are more cost-effective, require less time, can be placed by the surgeon at the end of the operation and may be associated with fewer complications [60]. The serratus anterior plane block is another regional technique with potential use in both VATS [61] and open surgery [62]. Liposomal bupivacaine is a slow-release bupivacaine preparation that shows promise when delivered as multilevel intercostal injections, potentially providing blockade of intercostal nerves for up to 96 hours [63, 64]. Randomized studies are awaited.

Perioperative Fluid Management

In lung resection surgery, the goal is to minimize the use of intravenous fluids while recognizing that the optimization of global and regional oxygen delivery is fluid dependent. Fluid management can be complex as overloaded patients are prone to develop interstitial and alveolar edema [65–68]. The presence of existing pulmonary disease, prior chemoradiotherapy, one-lung ventilation, direct lung manipulation by the surgeon, and ischemia-reperfusion phenomena can all lead to acute lung injury [69, 70]. Pneumonectomy patients are particularly at risk [71].

A volume-restrictive fluid regime of less than 3 ml/kg/h is usually recommended perioperatively, with a 24-hour positive fluid balance of less than 1500 ml (or 20 ml/kg/24 hr). The concern with such restrictive fluid management is that it may produce a hypovolemic state with impaired tissue perfusion, organ dysfunction, and acute kidney injury (AKI). The incidence of AKI is relatively common at around 5% [72]. Although restrictive regimes may result in perioperative oliguria, they are not associated with an increased risk of postoperative AKI [73, 74]. Similarly, setting a low perioperative urine output target (0.2 ml/kg/hr) or treating oliguria with fluid boluses does not appear to affect postoperative renal function [73–75]. The aim, therefore, is to maintain intraoperative euvolemia with a dry lung [76–78]. Over-restriction may eventually lead to organ dysfunction. Hypoperfusion can be avoided with the use of vasopressors and a limited amount of fluid to counteract the vasodilatory effects of anesthetic agents and neuraxial blockade [79]. Additional fluid can be given to compensate blood or exudative loss.

In line with other ERAS programs, balanced crystalloid is the intravenous fluid of choice [80]. In the immediate postoperative period, attention should also be paid to fluid balance and the patient's body weight. Oral fluids and diet should resume as soon as the patient is lucid and able to swallow.

Atrial Fibrillation Prevention

The onset of new postoperative atrial fibrillation and flutter (POAF) is common with an incidence of around 12% following lung resection [81, 82]. Risk factors include increasing age, male sex, Caucasian race, hypertension, COPD, heart failure, and valvular heart disease [81]. A more extensive operation (e.g., pneumonectomy) also increases the risk [82]. The development of postoperative complications is associated with a doubling of the incidence of POAF, while POAF itself increases the risk of stroke and in-hospital death [81].

Recommended prevention strategies for the development of POAF have been taken from the American Association for Thoracic Surgery (AATS) Guidelines [83]. If patients are taking β(beta)-blockers prior to surgery, they are at risk of developing POAF if withdrawn abruptly. Consequently β(beta)-blockers should be continued through into the postoperative period. In those patients who are magnesium deplete, intravenous magnesium may be given perioperatively. Digoxin is ineffective and should not be used. In patients deemed at particular risk of developing POAF, it is

reasonable to consider perioperative diltiazem (assuming the patient is not taking β[beta]-blockers and cardiac function is normal) or postoperative amiodarone. However, no clinical model has been developed to identify high-risk patients after lung resection, although the CHADS2 (Congestive heart failure, Hypertension, Age, Diabetes, and Stroke/TIA) score shows promise [84]. Furthermore, there is little evidence that POAF prophylaxis improves outcomes.

Surgical Technique

The majority of pulmonary resections worldwide are still performed via a thoracotomy, although minimally invasive techniques are increasingly popular. Acute and chronic postoperative pain is common with both open and VATS techniques and adds significant morbidity and healthcare costs.

Thoracotomy

Muscle-sparing and nerve-sparing thoracotomy techniques have been described in an attempt to mitigate the pain experienced as a result of chest wall damage, and both are recommended as part of an ERAS protocol if a thoracotomy is required [17].

A thoracotomy may be performed via a traditional posterolateral approach or via an anterior approach (axillary or anterolateral thoracotomy). Muscle sparing describes a thoracotomy in which there is not significant division of the latissimus dorsi or serratus anterior muscle fibers. A muscle-sparing incision is more often achieved via an anterior approach. The evidence for its use is somewhat mixed, but there may be improvements in short-term muscle function [85] and pain [86] for the first month.

Harvesting the intercostal muscle and bundle by separating it from both adjacent ribs in the line of the thoracotomy reduces postoperative pain compared to traditional thoracotomy techniques. The surgical retractor is then placed against bare bone, protecting the intercostal bundle from crush injury. The intercostal muscle can be divided to create a flap [87, 88] or left to dangle in the wound, further reducing pain [89].

Minimally Invasive Surgery

Minimally invasive surgery includes a number of techniques or approaches that involve video guidance for dissection, 1–4 ports, and no rib-spreading. Described techniques include multiport VATS lung resection, uniportal surgery (single-port VATS), and robotic surgery.

Observational studies of VATS lobectomy for lung cancer suggest better outcomes than an open thoracotomy. VATS is associated with less pain, better shoulder function, earlier mobilization, shorter length of stay, better preservation of pulmonary function, and better quality of life [90]. Five-year survival is also reported to be superior [91]. Nevertheless, there has been concern regarding the considerable selection and publication bias in the literature, with high-performing surgeons in high-performing centers responsible for many of the published retrospective studies. This has led some to ask whether the perceived benefits of a VATS lobectomy are due to the skill of the surgeon rather than the surgical approach [92].

The publication of the first large prospective study would appear to confirm the superiority of a VATS approach [52]. When compared to patients having an anterolateral thoracotomy, VATS patients had significantly less pain postoperatively and a shorter length of stay but no reduction in complications. A year later, advantages persisted with less long-term pain and improved quality of life. Recent large database studies using propensity matching seem to back up the findings of the superiority of VATS [93–95]. In one study of more than 28 thousand patients, there was a significant reduction in postoperative complications in favor of VATS. The benefits of a VATS approach are particularly evident in high-risk patients with poor predicted postoperative lung function [96].

A uniportal approach has been popularized with potential benefits purported to include less pain and discomfort. The rationale is that disruption of a single intercostal space with one port is less painful, but the counterargument remains that having a greater number of instruments through a single intercostal space is more painful than single instruments through multiple ports. One randomized trial failed to demonstrate any difference between uniportal and conventional multiport VATS lobectomy [97]. Postoperative pain, lengths of stay, and complications rates were equivalent.

A minimally invasive approach for pulmonary resections is recommended for early-stage lung cancer. Ultimately, the specific approach depends on the surgical team and their ability to complete the operation in an efficient and safe manner while respecting oncological principles.

Robotic Surgery

Robotic-assisted lobectomy has technical advantages over conventional VATS techniques. These include 7 degrees of movement, three-dimensional views, tremor filtration, motion scaling, and improved ergonomics. It is unclear whether this will translate into improvements in clinical outcomes. Studies have certainly demonstrated the feasibility and safety of the robotic approach, and morbidity rates appear equivalent to VATS [98–100]. As surgeons who have struggled with VATS are more likely to be comfortable with a robotic approach, this may allow more patients to undergo minimally invasive surgery.

Chest Drain Management

A chest tube or drain is necessary for the majority of cases following lung resection. Drains can cause pain and

inhibit pulmonary function, irrespective of the surgical approach [101]. Immobility and its deleterious effects are often seen as a consequence of conservative chest drain management strategies. Chest drain management is often crucial in determining the postoperative course of patients, influencing both the speed of recovery and the length of hospital stay.

Number of Chest Tubes

Historically, two chest tubes have been used to drain the pleural space after lobectomy, one at the apex to drain air and another at the base to drain fluid. Several randomized trials have now demonstrated that the use of a single chest tube is safe and effective. A single chest tube is associated with less pain and reduced chest tube duration without increasing the risk of recurrent effusion [102–104]. For routine cases, therefore, a single tube should be used instead of two.

Application of Suction

In theory, external suction applied to a chest drain promotes the apposition of pleural surfaces. This was thought to be important in facilitating the sealing of air leaks or ensuring adequate drainage of larger air leaks. However, concerns have been raised that bedside suction limits patient mobilization (by anchoring the patient to the bed space) and may actually potentiate air leak duration. Subsequently, a number of randomized clinical trials have been conducted comparing suction with no suction in the postoperative period.

The evidence is conflicting [105–108]. Nevertheless, there does not appear to be an advantage to the routine application of external suction in terms of shortening the duration of air leak, chest drainage, or length of stay. Therefore, since wall suction also limits patient mobility, its routine application should be avoided.

Digital Drainage Systems

Digital drainage systems are now widely available and may have several advantages over a traditional water seal. They are light and compact with a built-in suction pump. Consequently, they do not need to be attached to bedside wall suction should suction be required, favoring early patient mobilization. They are also able to objectively quantify the volume of air leak. The ability to store information and display trends of air leak over time allows more informed decision-making about chest tube removal and reduces inter-observer and clinical practice variability [109].

A recent meta-analysis compared digital and conventional chest drainage systems [110]. Overall, digital systems were associated with reduced chest tube time, length of stay, air leak duration, and costs. The use of digital drainage systems is to be recommended as they remove variability in clinical decision-making and facilitate early mobilization while positively influencing patient outcomes.

Pleural Fluid Drainage

Tradition dictates that the amount of pleural fluid output observed daily determines the timing of chest tube removal. Many surgeons have accepted arbitrary cutoff values (typically 200 ml/day) as a threshold below which it is safe to remove a chest tube. More aggressive chest drain removal strategies within fast-track programs have been shown to be safe. A non-chylous fluid threshold of 450 ml/day after thoracotomy was associated with only a 0.55% readmission rate for recurrent symptomatic pleural effusion [111]. A higher threshold of 500 ml/day following VATS lobectomy resulted in an incidence of clinically relevant recurrent effusions (needing drainage or aspiration) in only 2.8% of patients [112]. Therefore, it appears to be safe to remove chest tubes if the daily effusion is of a higher volume than traditionally accepted (up to 450 ml/24 hours) so long as there is no evidence of air leak, chyle, pus, or active bleeding.

Conclusions and Future Directions

A number of ERAS programs after thoracic surgery (principally lung resection surgery) have demonstrated improvements in outcomes. The recently published ERAS® Society guidelines should provide a framework for centers wanting to adopt ERAS within their institutions. Some of the recommendations are specific to thoracic surgery. Other recommendations are common to other specialty ERAS guidelines. Controversies still exist and there are instances where recommendations cannot be given on the current evidence, either because equipoise truly exists or because there is a lack of published evidence to support a particular intervention. Examples include whether volatile or intravenous anesthesia is more beneficial, advances in regional anesthesia, the role of non-intubated anesthesia, the optimal number of ports needed in a VATS approach to improve outcomes, and the emerging presence of robotic surgery in the treatment of lung cancer. It is hoped that the publication of the guidelines will harmonize the approach to the perioperative care of the thoracic surgical patient, encourage research where knowledge gaps or controversies exist, and promote collaboration between units.

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Enhanced Recovery in the Ambulatory Surgery Setting

54

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Introduction

Enhanced Recovery After Surgery (ERAS) pathways are a comprehensive approach to ensure patient safety before, during, and after surgery. Guidelines for many surgeries have specific ERAS components that ensure patients have optimal outcomes [1, 2]. This includes interventions such as carbohydrate loading, adequate hydration, avoidance and early removal of invasive devices, multimodal analgesia, early ambulation, and early oral intake. These pathways can significantly decrease hospital stay, reduce hospital costs, reduce postoperative complications, and maintain proper physiology. Many of these principles are applicable not only to patients undergoing major abdominal surgery but also to ambulatory (outpatient) surgery [3–5]. Essential principles of ambulatory surgery are shown in Table 54.1 and include preoperative, intraoperative, and postoperative considerations.

Preoperative Considerations

Patient selection is key to successful ambulatory surgery. Patient, surgery, and facility factors may influence decision-making. For example, the planned procedure should entail minimal blood loss and no specialized postoperative care, and postoperative pain should be manageable at home. Patients should be able to resume normal functions as soon as possible and should be mobile to at least some extent before discharge [6].

Patients should have stable and well-controlled medical conditions to avoid delayed discharge or perioperative complications and should have a responsible adult to take them home from the facility. Optimization of medical comorbidities is crucial to ensure safe patient care and to avoid unnecessary delays and complications. Patients who undergo high-risk surgery are often evaluated in a preanesthesia assessment clinic and may subsequently undergo medical optimization prior to their surgery in order to decrease perioperative risk. However, as ambulatory surgery is often considered lower risk and patients, on average, tend to be healthier, many may undergo a "virtual" or no formal preoperative evaluation at all. Ideally, their medical information is available to providers prior to the day of surgery so triaging decisions can be made in advance. On the day of surgery, these patients should be screened for cardiopulmonary disorders, obstructive sleep apnea, coagulation disorders, neuromuscular disorders, and endocrine dysfunction such as thyroid disease or diabetes, among other conditions that may significantly increase perioperative risk. If patients are found to be at high risk on the day of surgery or their medical conditions do not appear to have been optimized, a decision should be made on whether or not the patient should proceed to surgery [7].

Preoperative risk reduction should include recommendations for cessation of smoking up to 4–8 weeks prior to surgery. Quitting smoking even 24 hours before surgery can reduce carboxyhemoglobin levels, which can improve oxygen-carrying capacity and reduce pulmonary or cardiovascular complications. Patients will also experience less airway irritation, better wound healing, and have a lower risk of postoperative hypoxia as a result of airway blockade due to secretions [8]. Patients who are able to be contacted or seen in a preanesthesia clinic prior to surgery should receive recommendations to carbohydrate and fluid load the day before surgery. Measures as simple as drinking a carbohydrate drink or water (if clinically allowable and if there is no history of significant heart failure or chronic kidney disease)

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Table 54.1 Essential principles of ambulatory surgery [6]

Preoperative anesthesia assessment
Patient selection
(i) Surgical considerations (minimally invasive approaches)
(ii) Medical conditions
(iii) Social considerations and patient and family education
Anesthetic considerations
(i) Anesthetic history
(ii) PONV risk assessment
(iii) Airway assessment
Special considerations
(i) Elderly patients
(ii) Obstructive sleep apnea
Intraoperative anesthetic management
(i) General anesthesia
(ii) Regional anesthesia
(iii) Monitored anesthesia care
(iv) Multimodal analgesia and PONV prophylaxis
(v) Maintain normothermia
(vi) Antibiotic and venous thromboembolism prophylaxis (if indicated)
Postoperative management
(i) Postoperative pain management and treatment of PONV
(ii) Early postoperative mobilization
(iii) Discharge criteria and patient instructions
(iv) Post-discharge follow up

can reduce postoperative nausea and vomiting (PONV), modify insulin resistance, reduce infection rates and may contribute to improved wound healing [9, 10].

Furthermore, medication reconciliation is a vital part of ERAS protocols needed to ensure patients do not take medications the morning of surgery that place them at risk for postoperative complications and delayed discharge, such as certain antihypertensives and anticoagulants. Anticoagulation guidelines should be reviewed for all patients on blood thinners for the respective surgery and their comorbidities. PONV risk should be assessed using one of several tools, with the Apfel simplified score being most frequently used [11]. If the patient is found to be at higher risk (non-smoker, female gender, history of motion sickness, perioperative opioid use), proper pharmacologic prophylaxis should be administered both pre- and intraoperatively. PONV prophylaxis is necessary to promote early patient recovery, and routine multimodal antiemetic prophylaxis should be utilized in all ambulatory patients undergoing general anesthesia. A combination of dexamethasone (4–6 mg, IV, after induction of anesthesia) and ondansetron, a 5-hydroxytryptamine-3 antagonist, (4 mg, IV, at the end of surgery) may be used for most patients. Patients who are at a high risk of PONV may require additional antiemetic therapy both as prophylaxis and as treatment for established PONV postoperatively.

Benzodiazepines are sometimes administered to patients preoperatively for anxiolysis, either by request or clinical judgment, which can improve patient satisfaction. However, benzodiazepines should be used with caution in patients with a history of obstructive sleep apnea, dementia, and respiratory depression, as well as the elderly [12].

Patient education is an important component of ambulatory surgery [13, 14]. The patient should have a good understanding of the procedure and postoperative requirements and what the expectations are for recovery. The surgical process should be transparent, and the patient should be expected to be an active participant in their care. Furthermore, the patient's family should also be involved in this education process, and both the family and patient should have clear means of communication with the care team should they need further clarification, especially once they are discharged. One way to increase patient compliance is to provide both written and verbal instructions for care.

Intraoperative Considerations

Surgical approach and technique can impact ambulatory recovery. Minimally invasive surgical techniques should be used, and ambulatory surgery should not carry a significant risk of major complications. In fact, the anticipated degree of surgical trauma is more important for postoperative recovery than the surgical duration, and the surgeon should have sufficient experience with the procedure and a low complication rate record [6].

When the anesthesiologist prepares the anesthetic plan, care should be taken to keep postoperative stay in mind. This means using local or regional anesthesia whenever possible, using short-acting medications in the lowest doses for effective anesthesia and analgesia, proper reversal of muscle paralysis, and using medications that reduce postoperative nausea and vomiting and speed up recovery. Local anesthesia consistently has been shown to decrease postoperative pain and opioid consumption. Regional anesthesia does the same, with potential longer-lasting effects when postoperative regional catheters are placed [15, 16]. Although opioids may be necessary for surgical pain in many surgical situations, they should still be used judiciously, as opioid-related adverse events are one of the most common reasons recovery and discharge from the hospital are delayed. Non-opioid analgesics such as nonsteroidal anti-inflammatory drugs, acetaminophen, intravenous lido-

caine and field blocks, alpha-2 receptor agonists, gabapentinoids, and ketamine should be considered when clinically safe in order to decrease overall opioid consumption [17]. Regional anesthesia should also be utilized when indicated. Alternative non-pharmacologic modalities such acupuncture, reiki therapy, various relaxation techniques, and music therapy should be considered as well. In addition to proper analgesic choice, anesthetic choice should be tailored to decrease postoperative stay, which is a major goal of ambulatory surgery. Deep anesthesia should be avoided whenever possible in order to speed immediate postoperative wakening, ambulation, and oral intake and reduce pulmonary complications such as aspiration or respiratory depression [18–22]. PONV risk can be mitigated by minimizing the use of nitrous oxide, volatile anesthetics, high-dose neostigmine, and opioids.

Immediate Postoperative Considerations

Postoperative pain, nausea, vomiting, and respiratory depression should be adequately addressed, both clinically and pharmacologically. Ambulatory facilities should develop clinical pathways and protocols to manage common postoperative complications. Rescue analgesia such as intravenous or (preferred) oral non-opioid and opioid medications (when necessary) should be administered in order to prepare the patient for early ambulation and oral intake. It is essential to prepare patients psychologically for pain postoperatively; complete pain relief is not a realistic goal for every patient, and patients should be coached on pain management and proper postoperative expectations [11, 23]. Risk factors for postoperative pain include anxiety, preoperative pain, age, gender, surgery type, and various psychological factors.

If patients have refractory nausea and vomiting, repeating the same $5HT_3$ antagonist (i.e., ondansetron) in the recovery room may not be beneficial, and alternative medications such as promethazine, dimenhydrinate, dexamethasone, or scopolamine patches should be considered [11]. Respiratory depression is most commonly due to residual anesthetic effect, and proper airway protection, neuromuscular block reversal, and oxygen therapy should be ensured or administered in clinically appropriate scenarios. Patients with obstructive sleep apnea may be at higher risk for postoperative respiratory complications. These patients may benefit from the use of postoperative continuous monitoring especially if they receive opioids, continuous positive airway pressure device use, and opioid-sparing techniques such as regional anesthesia [24].

Post-discharge Considerations

To facilitate patient throughput, there should be a clear protocol for patient discharge in the ambulatory setting [25]. The Post Anaesthetic Discharge Scoring System (PADSS) and the modified Aldrete scoring system are commonly used tools to determine whether a patient is ready for discharge [26, 27]. Patients should also clearly understand their discharge instructions, medication plan, and who to contact should they need any clarification about their care.

The care of the patient does not end when they leave the hospital; rather, patients should be checked on the day after surgery or at least within 1 week by a healthcare practitioner to ensure proper healing, medication adherence, and pain control and return to usual daily activities. This can reduce repeat hospitalizations and emergency room visits, subsequently decreasing complications and associated healthcare costs. There are numerous benefits of improving early ambulation, including an early return to work, patient financial considerations, social considerations, and reduction of cardiovascular, coagulation, and respiratory complications. Early feeding should be ensured, along with the early return of bowel function and bladder function. If these physiologic parameters do not return to normal within 24–48 hours of surgery, there should be concern for urinary retention and ileus. Postoperative urinary retention is one of the main reasons for readmission, and it can cause urinary tract infections and permanent bladder injury, and usually requires urinary catheterization [28]. Currently the causes and treatment for postoperative urinary retention vary widely, and risk factors include age, preoperative urinary symptoms, prostate enlargement, spinal anesthesia, and high opioid use.

Postoperative fatigue can persist for weeks after surgery and can prevent the patient from returning to baseline function [29]. While it is still unclear how and why this phenomenon occurs, fatigue can be prevented by avoidance of deep anesthesia and reduction of opioid use. Perioperative neurocognitive disorder (PND) is another concern that presents as a decline in the patient's ability to perform complex cognitive tasks [30]. The cause of this phenomenon is multifactorial and may last for a long time before the patient regains their normal cognitive functioning. Some risk factors for PND include older age, abnormal baseline cognitive function, significant comorbidities, poor functional status, visual and hearing impairment, and neurodegenerative conditions [31, 32].

It is also possible that the patient may experience bleeding, hematoma, infection, and surgical wound healing issues, all

of which are other common causes of readmission following surgery [33, 34]. Patients should be clearly instructed for what to look for as a sign of infection (localized pain, redness, tenderness) and should be contacted after they are discharged home to ensure they are not experiencing any concerning symptoms.

Summary

Advancements in surgical and anesthetic techniques have enabled an increasing number of procedures to be performed on an ambulatory basis. For a successful ambulatory surgery program, important considerations include proper patient and procedure selection, choice of an anesthetic technique that facilitates rapid recovery and discharge, and ways to reduce complications and side effects such as postoperative nausea and vomiting, pain, and urinary retention. Multimodal analgesia is an important part of perioperative management, as well as patient education, optimization of medical conditions, and an interdisciplinary approach to help the patient return to baseline function as soon as possible.

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Enhanced Recovery After Surgery: Emergency Laparotomy

55

Carol J. Peden

Introduction

The term "emergency laparotomy" encompasses a surgical exploration of the acute abdomen for a number of underlying pathologies and is described by a large number of *International Statistical Classification of Diseases and Related Health Problems* (ICD-10) codes [1]; however, the commonest underlying pathologies are acute colorectal conditions [1–3]. The important difference between emergency laparotomy patients and patients undergoing elective intra-abdominal procedures is their presentation in a state of physiological derangement [1, 4]. The resource burden of emergency general surgery (EGS) is high. There are more patients that present each year in the United States with an EGS problem than present with a new cancer diagnoses, and this has increased annually since 2001 [5, 6]. In general, the sickest group of patients presenting with an emergency general surgical diagnosis are those undergoing emergency laparotomy.

The patients who undergo an emergency laparotomy are elderly, with the average age in major studies reported as between 62 and 67 years [2, 3]. These patients are likely to have comorbidities and between 20% and 50% present with systemic inflammatory response syndrome (SIRS), sepsis, and septic shock [1–7]. Although the underlying problems and surgeries performed vary slightly by country [1, 2, 8], common underlying causes for emergency laparotomy are intestinal obstruction, perforation, and exploratory laparotomy with or without wound debridement or abscess drainage [2]. Data from the UK National Emergency Laparotomy Audit (NELA) showed the commonest surgical procedures as adhesiolysis (16.8%), small bowel resection (16.2%), right colectomy including ileocecal resection (13.3%), and Hartmann's procedure (11.9%). Peptic ulcer suture or repair accounted for 5% of cases in the NELA audit [3]. More emergency patients undergo an open procedure than a laparoscopic procedure for comparable surgery in the nonelective setting [9]. Emergency laparotomy is one of the highest-risk surgical procedures, with data showing that about one in ten patients are dead 30 days after surgery, rising to one in four for those more than 80 years of age [3]. Complications are common and mortality increases until at least 1 year [10].

ERAS and Emergency Laparotomy

The international Enhanced Recovery After Surgery (ERAS) guidelines for emergency laparotomy are under development for publication and will provide detailed guidance on immediate preoperative management, intraoperative surgical and anesthetic management, and postoperative care. Many of the patients presenting for emergency laparotomy are elderly, and the guidelines will include sections on frailty, delirium, and end-of-life care. This chapter will summarize the background to the guidelines and discuss some of the studies that contributed to their development. As many components of colorectal ERAS pathways are applicable to emergency laparotomy patients, the details of the standard components will not be discussed in depth. The reader should refer to the relevant chapters of this book and ERAS guidelines [11].

Enhanced recovery programs based on a multicomponent pathway ranging from patient and family preparation in the community to rapid discharge following surgery may not seem an obvious fit for emergency general surgery [11]. However, the concept of ERAS, namely, that the patient is in the best possible condition for surgery within the limited time frame available, has the best possible management during surgery, and experiences the best postoperative rehabilitation, can still be applied. An approach to minimize the stress response to surgery with multidisciplinary delivery of key processes in defined time periods has been shown to benefit these high-risk patients.

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Until relatively recently there were very few studies focusing on improving the care of patients undergoing emergency laparotomy. The fact that these patients are acutely ill and present as emergencies with a multiplicity of underlying conditions has meant that this is a challenging group of patients for study with randomized controlled trials. In 2012, based on the poor outcomes highlighted in observational studies [2, 8, 12], a national audit was funded in England and Wales—the National Emergency Laparotomy Audit [3]—with the aim of capturing outcome and process metrics for all patients undergoing emergency laparotomy. Large-scale audits and cohort studies along with the development of consensus-based standards have helped define the deficits in care, highlight areas for improvement, and provide baseline data for research studies.

Background to the Development of an ERAS Approach for Emergency Laparotomy

A number of key papers published between 2012 and 2013 on large cohorts of patients from the United Kingdom, Europe, and the United States highlighted the extent of the problem for patients undergoing emergency laparotomy with mortality rates at that time of between 14% and 19% at 30 days, rising to 25% for patients more than 80 years of age [2, 7, 8, 12]. Other studies showed that a small number of EGS procedures accounted for a large number of deaths [6] and highlighted the difference between outcomes for emergency and elective general surgical patients [6, 7]. These reports and others highlighted a very variable delivery of care between and within organizations and also demonstrated that resource provision could make a difference to outcome [13].

A rising awareness that high-risk emergency general surgery patients deserved better care led to the publication of standards in the United Kingdom by the Royal College of Surgeons in 2011 for care of the high-risk surgical patients and emergency surgery [14]. Because of the lack of high-quality research in the field, this document was based on expert opinion but nevertheless provided important guidance on key components of care and suggested timelines in which that care should be delivered. The diagrams from the original Higher-Risk Surgical Patient document defining care pathways (recently updated in 2018 [15]) are similar to those in an ERAS pathway, and indeed the 2009 UK guidelines on implementation of enhanced recovery protocols stated that "every effort should be made to implement as many ERAS components as possible" for emergency patients [16]. Based on the recommendations in the original Higher-Risk Surgical Patient 2011 document and the 2009 ERAS guidelines, teams in the United Kingdom began to develop an ERAS approach to emergency laparotomy. Other centers around the world also began to apply their elective ERAS pathways to emergency patients and showed success [9, 17–22]; for example, an ERAS program for emergency colorectal tumor resection was associated with a significantly shorter length of hospital stay and faster recovery of bowel function with no change in 30-day mortality and readmission [17]. Many of these studies were relatively small and often excluded sicker patients [9, 17, 18]. Other recent papers discussing emergency surgery and an ERAS approach have measured delivery of a standard colorectal ERAS pathway in emergency patients [23]. Unsurprisingly, compliance was highest with the intraoperative processes of an elective pathway [9, 23]. Application of an elective ERAS pathway appears to be effective, but there are other dimensions of care that should also be delivered to the emergency ERAS patient; these have been summarized in recent reviews and editorials [24, 25], and key components are discussed below.

Management of Physiological Derangement

Many of these patients present with significant physiological derangement including a marked stress response, gut dysfunction, insulin resistance, fluid shifts, SIRS, and with up to 40% of patients having a septic focus [1, 4]; the presence of hypotension secondary to sepsis has a particularly poor outcome. The physiological derangement requires early diagnosis and active management. Studies have shown an association between early risk scoring, active management, and a reduction in mortality [3, 22]. Monitoring of blood lactate as a marker of risk [26], and in monitoring of response to resuscitation in line with the Surviving Sepsis guidelines [26, 27], has been used [3, 22].

Diagnosing and Treating Sepsis

An ERAS approach to emergency laparotomy should have as a central pillar an active and aggressive approach to seeking out sepsis and rapid treatment when appropriate with antibiotics and source control in line with the 1-hour bundle of the Surviving Sepsis guidelines (Table 55.1) [3, 15, 24–27]. A delayed response increases mortality as does failure to manage in accordance with appropriate guidelines [15, 26–28]. Large numbers of laparotomy patients have sepsis at presentation, and yet one large audit of emergency general surgery patients recorded the median time to source control as 19.8 hours [29]. The component most likely to be missed from early sepsis management was acquiring blood cultures.

Early Surgery and Source Control of Sepsis

There is a variety of different evidence and recommendations in the area of early surgery and sepsis control, which is well summarized in the 2018 High-Risk Surgical Patient

Table 55.1 The 1-hour sepsis bundle. The presence of sepsis should be considered in all emergency surgery patients at presentation. A proactive approach to resuscitation with the sense of urgency required to meet the 1-hour sepsis bundle components [26] is necessary for all emergency surgery patients with signs of sepsis

Measure lactate level. Remeasure if initial lactate is >2 mmol/L
Obtain blood cultures prior to administration of antibiotics
Administer broad-spectrum antibiotics
Begin rapid administration of 30 ml/kg crystalloid for hypotension or lactate ≥4 mmol/L
Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥65 mm hg

Reprinted with permission from Levy et al. [26]
"Time zero" or "time of presentation" is defined as the time of triage in the emergency department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements of sepsis (formerly severed sepsis) or septic shock ascertained through chart review

document from the Royal College of Surgeons in the United Kingdom [15]. This document provides some bundles and timelines for patients presenting to an emergency general surgical service. These bundles are for emergency, immediate, and non-immediate surgery and nonoperative care. Recommendations are made that all patients should be managed in accordance with the "Surviving Sepsis" protocol [27], and source control for patients with septic shock by surgery or other means (such as interventional radiology) should begin immediately upon clinical diagnosis and be well underway within 3 hours. For patients with sepsis without septic shock, source control should occur within 6 hours. A number of papers suggest that the prioritization of EGS patients to early surgical intervention has been shown to significantly reduce mortality and morbidity, particularly in patients with perforated gut [30, 31].

The Role of Risk Assessment

Risk assessment has become an important tool in the management of the emergency laparotomy patient [15]. Risk scoring was promoted in the first Higher-Risk Surgical Patient document [14], as so many laparotomy patients were not receiving care appropriate to their risk, such as planned admission postoperatively to an intensive care unit (ICU). Clinical teams, inexperienced in management and without widespread knowledge of the outcomes of emergency laparotomy, underestimated the great potential for poor outcome. Having a risk score facilitates communication among clinical teams about priorities and pathways and helps direct discussion with the patient and family. There are a number of surgical- or disease-specific risk prediction tools [32–35]. Some, such as P-POSSUM (Portsmouth-Physiological and Operative Severity Score for the enumeration of Mortality and morbidity) [33], were developed many years ago for retrospective comparison of observed and expected outcomes, when the values of all variables are known, and there is some concern about overinterpretation for individualized patient preoperative prediction when some variables must be estimated. Risk prediction scores give a population risk based on a risk model. However, scores can over- and underestimate risk for individual patients. An example is a patient with a perforated peptic ulcer, who is acutely unwell with markedly deranged physiology and a very high risk score, but who may benefit from rapid relatively simple surgery.

A large number of patients in the NELA database and the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP®) database have allowed development of specific risk tools for emergency laparotomy patients, which more consistently predict the actual risk of emergency laparotomy for high-risk patients [34, 35]. When a risk score was calculated retrospectively on patients in the NELA dataset who had not been risk scored preoperatively or at the end of surgery, those patients had poorer outcomes than a risk-matched cohort who had prospective risk scoring performed [3].

Goal-Directed Fluid Therapy

Goal-directed fluid therapy in emergency laparotomy patients is, at the time of writing, the subject of a major randomized controlled trial FLO-ELA [36]. A Cochrane systematic review showed no benefit on mortality of increasing perioperative blood flow using fluids with or without inotropes or vasoactive drugs [37], although only 2 studies of emergency surgery with only 130 patients were included in the analysis. Despite no reduction in mortality, a reduction in complications and length of stay was seen. The OPTIMISE study showed no benefit in outcome when use of a cardiac output-guided hemodynamic algorithm was compared with normal care in high-risk patients undergoing major gastrointestinal (GI) surgery. However, when the OPTIMISE results were incorporated into an updated meta-analysis, the intervention showed a reduction in complication rates [38]. Goal-directed fluid therapy should be considered on a case-by-case basis for patients undergoing emergency laparotomy.

Postoperative Management in a Critical Care Bed

Even with the best reported results for emergency laparotomy with an average 30-day mortality of around 5% [39], death rates are still up to five to six times higher than patients undergoing elective colorectal surgery. Despite this disparity, it still seems that pathways for elective patients undergoing major surgery routinely include critical care postoperatively, while this is not always the case for patients undergoing emergency laparotomy [40]. Large database analyses have shown associated worse outcomes with lower numbers of ICU beds and less imaging resources [1, 41]. Patients with a planned admission to critical care after emergency laparotomy do better than those going to a less resourced area, and those that are returned to a ward or floor

area after surgery and then require escalation to critical care do very poorly [42]. "Failure to rescue" is a significant contributor to mortality [43], and this group of patients is at such risk of complications that they should be managed postoperatively in an area with close observation, with skilled nurses and physicians available to respond immediately to deterioration. If ICU beds are unavailable, then a plan should be made for postoperative management that takes into account these patients' high risk—this could include prolonged management in a postoperative recovery area.

ERAS Approaches with a Focus on Rapid Management of Physiological Derangement and Sepsis and Reliable Delivery of Evidence-Based Care

A Danish study used a perioperative care protocol to improve care in the treatment of perforated peptic ulcer—a condition with substantial morbidity and mortality and a frequent presentation in which the patients are acutely unwell and septic [20]. The intervention included evaluation and risk stratification, minimization of surgical delay, and early use of broad-spectrum empirical antibiotics preoperatively. Postoperative components delivered were respiratory and circulatory stabilization in a high-dependency unit, a focus on administration of nutrition and fluids, appropriate analgesia, and early mobilization. Mortality was reduced by one-third, to 17% in the intervention group compared with 27% at 30 days in the control group. Another Danish study [21] implemented a multidisciplinary perioperative protocol in patients undergoing emergency laparoscopy and laparotomy. Components included early resuscitation and antibiotics, surgery within 6 hours, and monitored care postoperatively for at least 24 hours. Mortality at 30 days decreased from 22% in the control group to 15% in the intervention group.

A group of four UK hospitals with experience in enhanced recovery developed a care bundle approach to provide a pathway of care that emphasized rapid and timely management of emergency laparotomy patients with the aim of ensuring optimal management throughout the care pathway [22]. A six-point, evidence-based care bundle was used. The bundle included prompt measurement of blood lactate, early review and treatment for sepsis, transfer to the operating room within defined time goals after the decision to operate, use of goal-directed fluid therapy, admission to an intensive care unit postoperatively, and multidisciplinary involvement of senior clinicians in decision and delivery of perioperative care. The implementation project and care bundle was called the Emergency Laparotomy Quality Improvement Care Bundle or "ELPQuIC" for short. Implementation of ELPQuIC, using an ERAS approach with continuous quality improvement, led to increased delivery of key processes of care and reduced risk-adjusted mortality significantly. Improvement in mortality continued after the end of the project, and economic analysis showed that despite the increased use of resources (ICU for many more patients and goal-directed fluid therapy), there was no increase in costs [44].

The Emergency Laparotomy Collaborative (ELC) [45] study scaled up the ELPQuIC study across 28 hospitals. ELC differed slightly from ELPQuIC in that the study had much greater funding and quality improvement support, which allowed participating teams to be coached on quality improvement, leadership, and change management. In addition, there was greater emphasis on the management of sepsis (Fig. 55.1) [22, 45]. There were 5562 patients in the baseline ELC group before implementation of the ELPQuIC bundle and 9247 patients in the post-implementation group. Unadjusted mortality fell from a baseline of 9.8% to 8.3% in the 2nd year of the project. Mean length of stay reduced from 20.1 days to 18.9 days (length of stay tends to be long in the United Kingdom as acute skilled nursing facilities are not commonly used). Significant improvements in five out of six items in the care bundle delivery were achieved. This study confirmed the changes seen in the ELPQuIC project and in the National Emergency Laparotomy Audit [3, 22], namely, improvement in delivery of key processes in an emergency surgery pathway is possible and that this is linked to improvement in patient outcomes.

Other Significant Considerations in Delivery of an ERAS Approach for Emergency Laparotomy

The Elderly

All the large studies show that age is significantly associated with poor outcomes for emergency laparotomy patients; indeed one NSQIP study showed a 90% mortality at 30 days for patients more than 90 years of age [2]. Although average mortality has reduced year on year in the National Emergency Laparotomy Audit from 11.8% for 2014 to less than 10% for 2017 data, mortality for patients older than 80 in particular remains very high at 17% at 30 days and 22% at 90 days [3]. Clearly the risk for these patients is so high that if surgery is to be performed, meticulous delivery of all evidence-based pathway components is essential. Many of these patients will be frail, resulting in a lack of resilience in the face of a physiological insult, and a validated frailty assessment [15, 46] should be performed if possible, acknowledging the limitations in the acute environment, along with a simple assessment of cognitive function [47]. Frail patients and those with cognitive dysfunction have a high risk of mortality and morbidity, which will not be captured by the commonly used surgical risk scores [15, 48]. Involvement of a care-of-the-elderly physician to co-manage these patients should occur as soon as possible and is associated with better outcomes [49], although at present the evidence that this actually occurs is low [3]. Patients

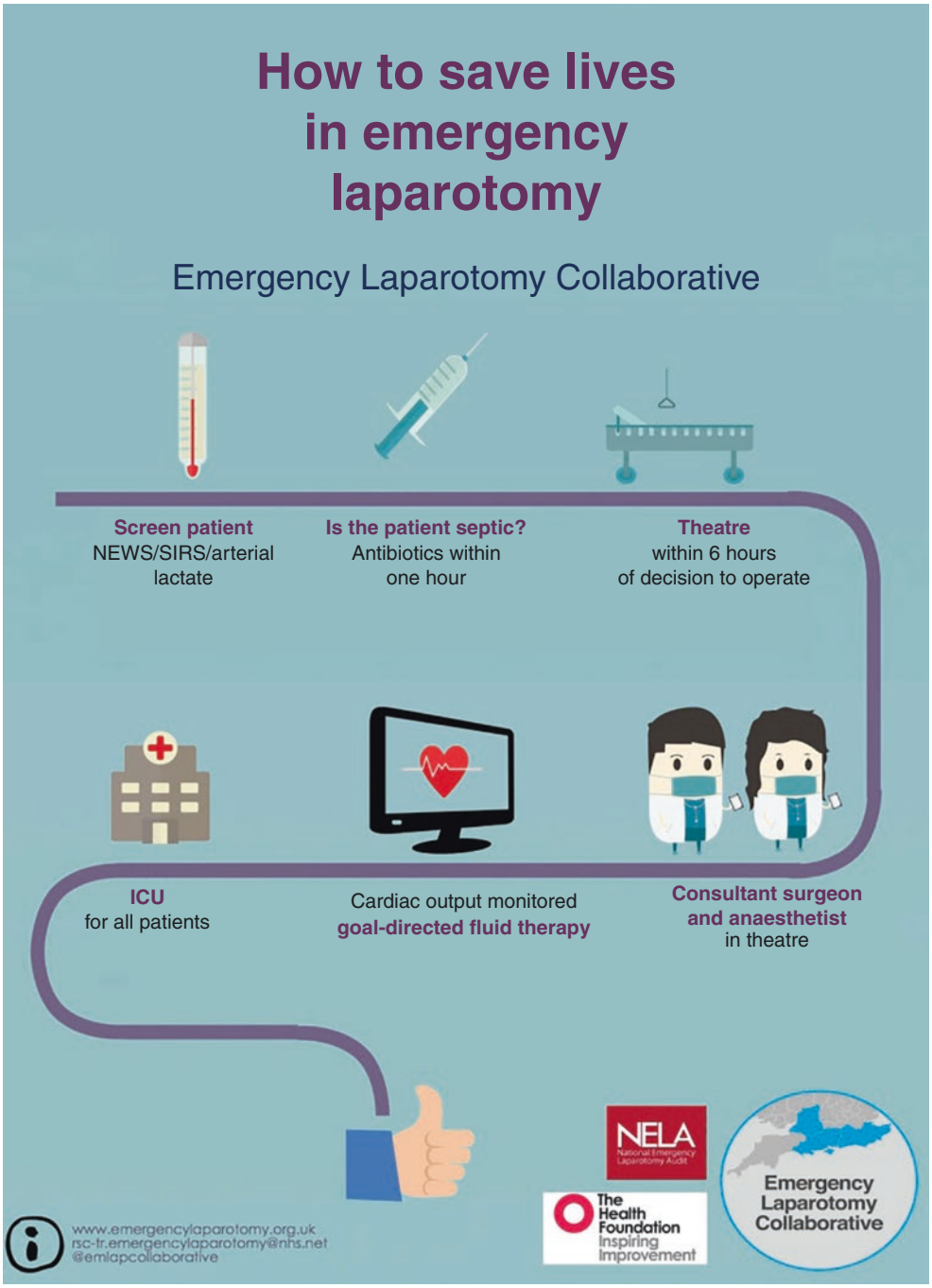

Fig. 55.1 The pathway of care used in the Emergency Laparotomy Collaborative [45]. A scaled-up program based on the ELPQuIC bundle [22]. (Reprinted with permission from Aggarwal et al. [45])

should be monitored regularly for delirium with an awareness that hypoactive delirium occurs more commonly than an agitated delirious state and has a poorer outcome. The American College of Surgeons and the American Geriatric Society have joint guidelines on how to prevent, diagnose, and care for delirium in the surgical patient [50]. Incorporation of a "Hospital Elder Life Program," with simple measures such as mouth care and regular orienting communication with patients, for those undergoing major intra-abdominal surgery demonstrated a significant reduction in the incidence of delirium [51].

Patient and Family Involvement and Shared Decision-Making

The large cohort studies of emergency surgery show that some patients undergo major surgery in circumstances where they are at very high risk of perioperative death. Such patients include the elderly with severe comorbidity, the frail, and patients with severe life-limiting illnesses [2, 10, 46, 48, 52]. Emergency abdominal surgery for perforation or obstruction is a not uncommon mode of death for patients with disseminated cancer [53]. For the very high-risk patients who survive surgery, survival might mean a prolonged hospital stay

with multiple complications. For some patients surgery may be futile; for others, such as those with a peptic ulceration, rapid surgery may lead to a good outcome. The data on 90-day and longer outcomes and particularly patient-reported outcomes is lacking. For some patients, quality of life and retaining independence for as long as possible are paramount. Surgery may offer a "quick fix," but in very high-risk patients, surgery should not be undertaken without discussion about ceilings of care, even though this is challenging in the acute situation [15, 52]. There is guidance available to surgical teams to help manage these situations, and patient satisfaction with emergency abdominal surgery is associated with receiving sufficient information about the risks and benefits of surgery [52–54].

Emergency General Surgery Service Provision

The specialty of EGS is developing around the world [55], but it is still very possible to have complex colorectal surgery performed on a critically ill patient by a surgeon whose main expertise is in breast surgery. The fact that these procedures are emergencies and that surgery is often performed out of hours, or during the day by teams juggling multiple other commitments, adds to the patients' risk. There is mounting evidence to show that availability of acute care surgeons improves outcomes in patients requiring emergency laparotomy [41, 55]. The availability of surgical teams to manage these complex patients may be improving with the development of the specialty of emergency surgery. However, despite EGS being one of the highest-volume specialties, many centers still lack a dedicated EGS service [15, 55]. Delivery of an enhanced recovery approach to emergency laparotomy by a senior team available to act rapidly when needed has been shown to improve outcomes [41, 55, 56].

A Framework for an Enhanced Recovery Approach to Care of the Patient Undergoing Emergency Laparotomy

From the studies to date and current developments in perioperative care, the following principles should be applied for an ERAS approach to emergency laparotomy. All patients should be managed according to a standardized pathway, with senior multidisciplinary team involvement and regular review of outcomes. The pathway of care should be developed with input from the emergency department, radiology, hospitalists, intensive care, and care-of-the-elderly physicians, as well as surgeons and anesthesiologists [3, 15].

Preoperative Principles

- Rapid assessment of the patient for physiological derangement using a validated method such as an early warning scoring system. Abnormal scores should trigger rapid escalation in line with pre-established protocols, while awaiting surgery patients should have regular reevaluation [15, 20, 24, 25].
- Resuscitation and correction of underlying physiological derangement where possible should begin immediately and consider use of lactate as a measure for resuscitation [15, 22, 26, 27].
- Immediate evaluation of all patients for sepsis using a validated sepsis score [26, 27].
- Rapid administration of antibiotics when signs of sepsis are present and performance of the 1-hour sepsis bundle [26, 27].
- Early computed tomography (CT) scan as needed, with immediate review by senior radiologist [3, 15].
- Use of a validated risk-scoring tool to inform pathways of care and shared decision-making with the patient and family [3, 15, 32–35].
- Patients more than 65 years of age should be assessed for frailty using a simple validated frailty score and have a simple evaluation of cognitive function performed [3, 15, 46–48]. Abnormalities in any of these parameters should trigger referral for evaluation at the earliest possible opportunity by a care-of-the-elderly physician [49]. All patients, but particularly those who have an abnormal performance on a cognitive function test, should be allowed to retain hearing aids and glasses and have a family or a friend present for as much time as possible prior to surgery [50]. Drugs that meet the Beers criteria, such as benzodiazepines, should be avoided at all points in the perioperative pathway in an effort to reduce delirium [57].
- Early involvement of senior surgeons and anesthesiologists with resuscitation and planning of care. Involvement with the ICU team early, ideally before surgery if mortality risk is high.
- Surgery within a defined time period depending on urgency but at least within 6 hours after the decision to operate. When the patient is to be managed conservatively, such as for bowel obstruction, regular review using objective measures should occur [15].
- Where possible, patients should be given appropriate information, education, counseling, and shared decision-making appropriate to their risk [52–54].

- Other preoperative ERAS components such as carbohydrate loading and venous thromboembolism (VTE) prophylaxis should be considered on a case-by-case basis. However, the benefit of these components should be considered for every patient [11].
- An NG tube may be required preoperatively depending on the underlying pathology.

Intraoperative Care Principles

- Surgery and anesthesia by consultant/attending staff in recognition of the high risk of mortality and morbidity of patients undergoing emergency laparotomy [3, 15].
- Damage limitation surgery where appropriate, recognizing that the acute patient is in a state of physiological derangement and that there is an association with increasing length of surgery and poor outcomes, particularly in the older patients [55, 56].
- Nasogastric (NG) tube should be placed and managed as appropriate depending on underlying pathology.
- Fluid resuscitation guided by hemodynamic algorithms assessed on a case-by-case basis and in line with local protocols [4, 11, 15].
- Active warming and glucose control [4, 11].
- Anesthesia with short-acting agents [4, 11].
- Analgesic use with opioid-sparing techniques including local anesthetic blocks where appropriate. The use of epidural anesthesia is controversial in this patient group as placement may be difficult in the presence of an acute abdomen and the incidence of active sepsis is high [4].
- Postoperative nausea and vomiting prophylaxis as appropriate.
- Neuromuscular blockade to facilitate surgical access, with monitoring. If the patient is to be extubated at the end of the procedure, full reversal should be established with a peripheral nerve stimulator as this patient group is at high risk for aspiration [4].
- Drains should be avoided if possible [11].
- Reassessment of risk at the end of surgery and a repeat blood lactate to inform postoperative management [3, 15].
- Risk assessments before and at the end of surgery should be used not only to re-evaluate the patient's condition but to inform a standardized approach to care and to facilitate communication about the patient between multiple teams [3, 15].

Postoperative Management

- These patients have a high risk of major morbidity and mortality and should therefore be managed in a critical care bed. If critical care beds are unavailable, the patient's risk score should dictate pathways of care, but a period of extended recovery should be provided at a very minimum [3, 15, 22, 24, 25].
- These patients are likely to require close monitoring for several days following surgery as their risk of complications and death is so much higher than elective patients undergoing comparable surgery [2, 7].
- Postoperative fluid management may be complex due to ongoing fluid, and electrolytes shift from physiological derangement [4]. Ongoing fluid management in a monitored environment should be considered until the patient is drinking.
- Postoperative diet and bowel regimen management should occur in line with ERAS principles and be assessed on a case-by-case basis dependent on original pathology [11].
- Early mobilization strategy may be particularly important in these patients who may have been septic and therefore at high risk of muscle catabolism [58].
- Postoperative NG tube may be required depending on underlying pathology but should be removed as early as possible.
- Opioid-sparing analgesia. Emergency laparotomy patients are likely to be at increased risk of renal dysfunction, and so nonsteroidal analgesics should be used with caution.
- Removal of urinary catheter, consider from day 1 dependent on patient status.

There are studies that demonstrate that functional recovery after the first postoperative day is similar in elective and emergency colorectal patients [9, 19]. Early removal of drains and catheters, avoidance of excess intravenous fluid administration, and limitation of opioid analgesics to the immediate postoperative period, in line with ERAS principles and evidence-based practice, have been shown to significantly reduce major complications in emergency surgery patients [19]. The majority of studies that have occurred for laparotomy patients with an ERAS approach have shown a reduction in major complications [17, 19]. When major complications occur, the association with subsequent poor outcome over an extended postoperative time is well recognized [59, 60]. For this elderly, fragile group of patients who may have "one shot" to get it right, using an ERAS approach seems highly logical.

Implementation

Implementing an enhanced recovery pathway, especially for a complex area such as emergency surgery, is very challenging.

The EPOCH study, a major study delivering a 37-component evidence-based pathway to emergency laparotomy patients across 90 hospitals, was fully funded to have ethnographers (a type of clinical anthropologist) study how and why attempts to implement the pathway succeeded or failed within a subset of hospitals participating in the trial [61–63]. The study found that clinicians lacked dedicated time to work on improvement and needed to change management skills to persuade all members of the multidisciplinary team to alter traditional pathways. Teams felt that segmenting the pathway into project areas—for example, preoperative, intraoperative, and postoperative work groups—and working on a small number of critical processes were helpful. Lessons from the EPOCH study suggest that if data is to be collected to support implementation, it should be parsimonious and should be automated if at all possible. Time for improvement and coaching in quality improvement and change management helps support pathway delivery, and senior executive buy-in is essential to help provide these resources. A Delphi study on training for, and implementation of, enhanced recovery pathways supported the findings in the EPOCH study [64]; audit and data support were deemed very important, as was management buy-in and senior clinical leadership. An ERAS nurse or facilitator with dedicated time, communication about the ERAS pathway, and effective multidisciplinary team working was also seen as central to successful implementation. Reliable delivery of the six bundle components featured in ELPQuIC [22] and ELC [45] may have been easier to implement than a much larger pathway—suggesting, at least initially, that teams attempting to implement an ERAS emergency laparotomy approach should focus on a few key components (Fig. 55.2) [62, 63].

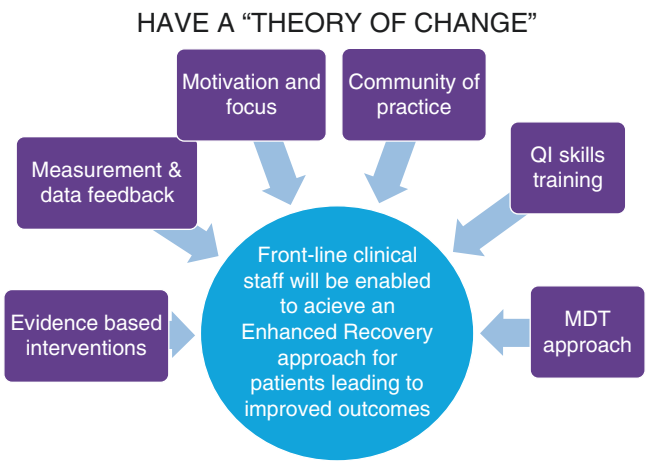

Fig. 55.2 A conceptual approach to the "theory of change" required to successfully implement an evidence-based pathway for emergency laparotomy [62, 63]. MDT multidisciplinary team, QI quality improvement. (Adapted from Stephens et al. [63])

Audit and Outcomes

Having a defined ERAS pathway for management of emergency laparotomy patients facilitates audit, measurement, and subsequent improvement (Fig. 55.3). Emergency surgery has traditionally suffered from the fact that different teams manage the patients on an occasional basis without real ownership of outcomes. The establishment of audits focused on this high-risk group has helped improve the profile of laparotomy patients [3] but still shows that development of a formal pathway with regular multidisciplinary feedback is not the norm. As many of these patients are very high risk, using a structured mortality review proforma, which asks specific questions about where gaps in care occurred or where communication could have been better or intervention more timely, and reviewing the findings regularly may be more effective than the more traditional morbidity and mortality review [65].

Audit can focus on a "structure, process, outcome" [66] approach with analysis of structure covering service delivery, for example, availability of staff, operating rooms, and intensive care beds. Process measures can include percentage of times key processes were delivered, such as antibiotics within 1 hour of diagnosis of sepsis. Outcome metrics should not only include mortality length of stay and readmissions but also measure common complications and patient experience. As emergency laparotomy patients continue to die in the months following surgery, mortality should be collected when possible at intervals at least up until 1 year [10]. Economic analysis is helpful to make the business case to implement an ERAS approach for emergency patients. The few studies that have been done show the approach is effective with economic benefit from reduced length of stay and complications. More studies are needed.

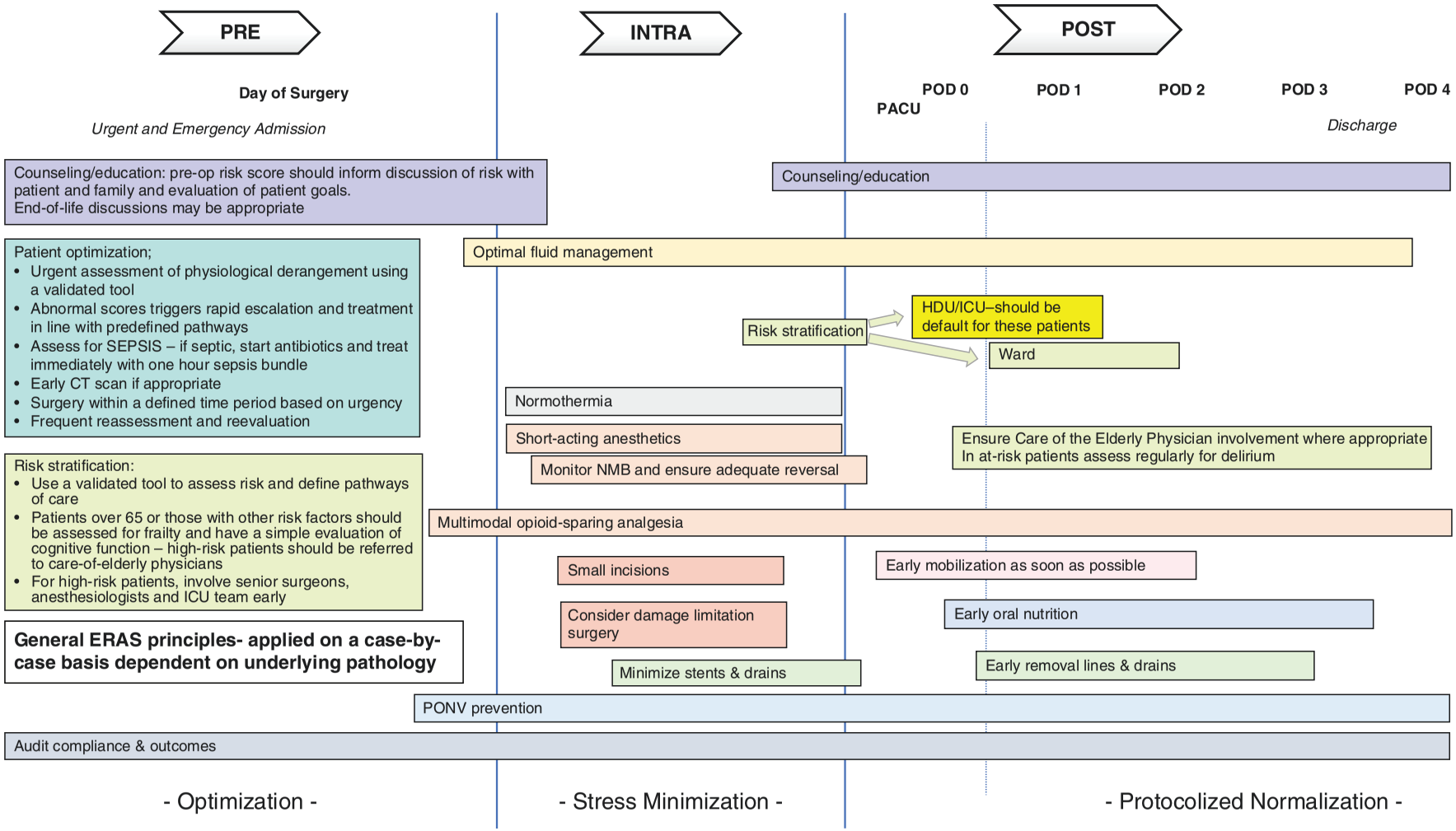

Fig. 55.3 An ERAS approach to emergency laparotomy, applied on a case-by-case basis dependent on underlying pathology. Abbreviations: CT computed tomography, PACU postanesthesia care unit, HDU high-dependency unit, ICU intensive care unit, NMB neuromuscular blocking agents, PONV postoperative nausea and vomiting

Audit serves little purpose if the results are not used to improve care. To that end, teams should have a process to share key metrics widely among all teams involved in patient care, which can include surgeons, anesthetists, operating room (OR) staff, emergency department teams, and care-of-the-elderly physicians. Run charts or time series charts of performance should be displayed to maintain motivation and to celebrate success when improvements have occurred [67].

Conclusion

Applying the concepts of an enhanced recovery approach has helped change the management of this high-risk patient group by delivering a standardized evidence-based pathway with urgency and proactive management of physiological derangement rather than allowing a traditional approach with delays and a focus on the wide variations in patient presentation and underlying intra-abdominal pathology. ERAS has supported a much needed paradigm shift in the management of these surgical patients, with dedicated teams, early evidence-based resuscitation using "Surviving Sepsis" guidelines, early antibiotics, early surgery, damage control laparotomy, and postoperative care in the intensive care unit.

A great deal of progress has been made in recent years in the management of patients undergoing emergency laparotomy, with resultant improved outcomes. Part of the improvement in outcomes is due to better data and a much greater understanding of the high risk of mortality and morbidity these patients face in comparison with those undergoing a similar procedure electively. The growth of enhanced recovery protocols over the same time period as the growing interest in emergency laparotomy has helped frame a new way of managing these patients. With great patient complexity, out-of-hours presentation, and the involvement of multiple different clinical teams, a standardized approach offers simplicity and guidance to all those involved in care. Adoption of an ERAS emergency laparotomy pathway requires not just a pathway but an implementation science approach to delivery. Outcomes are improving and in some centers have improved dramatically. Challenges remain, such as the need for greater understanding of long-term outcomes including patient-reported outcomes and better prognostic indicators for those patients in whom surgery is futile.

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Liver Surgery

56

Ismail Labgaa and Emmanuel Melloul

Introduction

Liver surgery is a major and challenging procedure. Major morbidity ranges from 17% to 27% in malignant disease, with a mortality risk up to 5% [1]. Pulmonary complications mainly related to the vicinity of the liver with the diaphragm may reach 30% with increased risk of thromboembolic events of 5% [1–4]. In addition, about 50% of patients experience adverse digestive events [5]. Perioperative stress is increased during major liver surgery, and all measures implemented to reduce the metabolic stress response could potentially reduce postoperative complications [6]. Several meta-analyses confirmed that the use of an enhanced recovery program significantly reduces hospital stay, cost, and postoperative complications compared to traditional care, providing good adherence (compliance) to the enhanced recovery after surgery (ERAS) protocol [7–9]. The ERAS® Society liver study group has recently published the guidelines for perioperative care for liver surgery [10]. Sixteen out of the 23 standard items of ERAS were studied for liver surgery. The highest level of evidence (level 1 or 2) was available for only five items (i.e., perioperative nutrition, prophylactic nasogastric intubation, postoperative artificial nutrition, prevention of delayed gastric emptying, and stimulation of bowel movement). In this chapter, we will highlight specific ERAS items that are paramount for liver surgery, namely, fluid balance management, minimally invasive approach, prophylactic abdominal drainage, postoperative glycemic control, use of nasogastric tube decompression, and epidural analgesia (Fig. 56.1).

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Fluid Balance and Electrolyte Management

Fluids shifts occur following liver surgery given the need for low central venous pressure (CVP). The reduction in hepatic venous congestion by careful control of CVP during hepatic resection is associated with a reduction in intraoperative blood loss [11–13]. Maintenance of euvolemia is critical to preserve renal function and prevent ascites. The management of fluid following liver surgery includes commonly large volume fluid resuscitation in the initial 24–48 hours post resection, followed by aggressive diuresis in order to minimize electrolyte shifts. This is more evident in cirrhotic livers, which are more vulnerable to fluid shifts. To achieve adequate fluid balance, patients undergoing surgery within an ERAS protocol should have an individualized fluid management plan. As part of this plan, excess crystalloid and blood loss should be avoided in all patients. It is more likely that a synergistic combination of CVP monitoring and measure of stroke volume variation (SVV) methods should be the standard form of hemodynamic monitoring in liver surgery. In a recent review by Hughes et al., the maintenance of a low CVP is associated with reduced blood loss and blood transfusion rates [14].

Goal-directed fluid therapy at the end of hepatic resection and during the first 6 hours enables a faster restoration of circulating volume with reduction in complications [15]. The use of balanced crystalloid rather than 0.9% normal saline to maintain intravascular volume is strongly recommended to avoid hyperchloremic acidosis and other causes of postoperative morbidity [10]. The role of colloids remains controversial, and the use of hetastarches increases the risk of renal dysfunction when systemic inflammatory response syndrome (SIRS) and sepsis are present and should be avoided in liver resection [16]. Some authors use blood urea nitrogen (BUN) as a measure of adequate fluid resuscitation and try to ensure that patients gain no more than 5% of their preoperative weight [17]. Therefore, close monitoring of postoperative body weight is paramount, particularly in the first 48 hours.

Hypophosphatemia is also a commonly observed phenomenon after a major liver resection and is associated with

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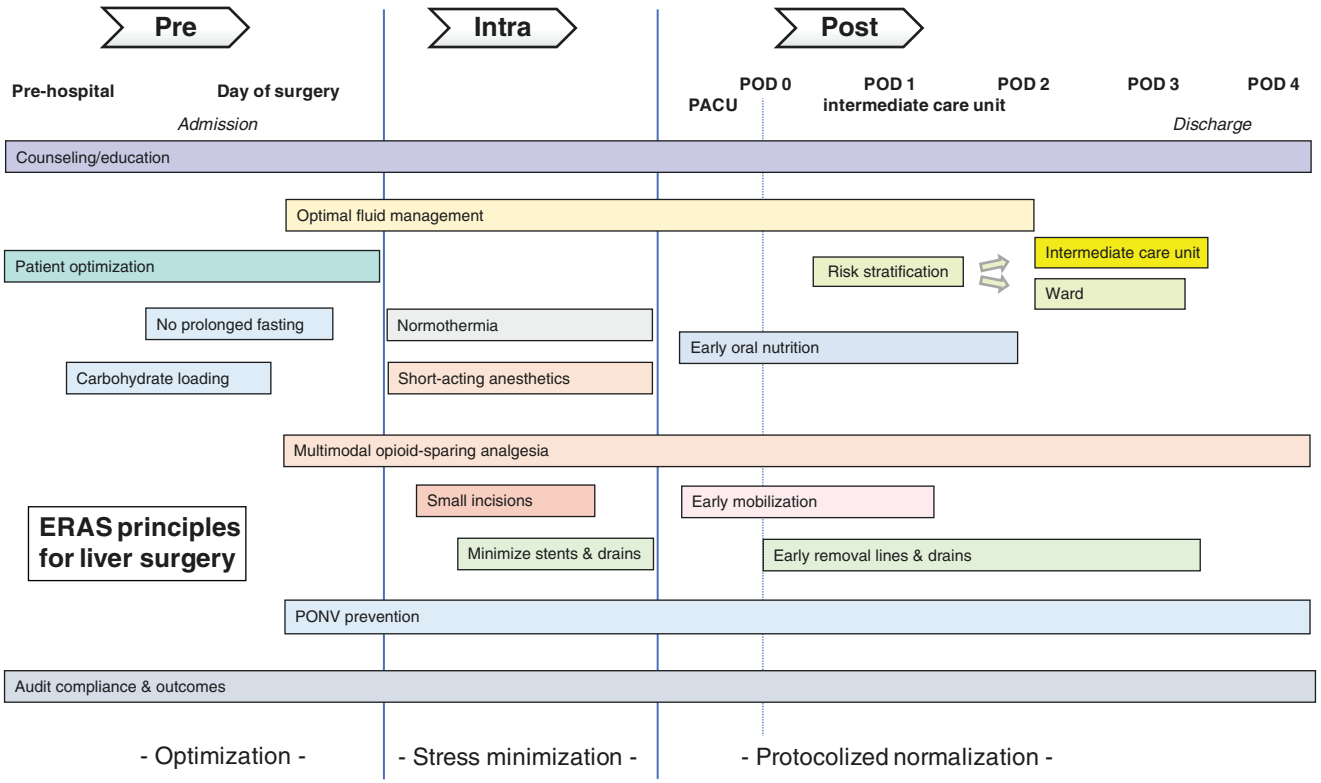

Fig. 56.1 ERAS principles for liver surgery. POD, postoperative day; PACU, postanesthesia care unit; PONV, postoperative nausea and vomiting

increased morbidity and mortality [18]. Compared to the preoperative level, there are two drops observed in serum phosphorus within 2 and 48 hours of surgery [17]. According to two recent studies, patients reach their nadir level on postoperative day 2, which slowly rises to the normal phosphorus range between postoperative days 3–4 [17, 18]. It seems that major and minor resections show similar pattern decline through postoperative day 2; however, the serum phosphorus level recovers more quickly after minor resections. In a recent study by Squires et al., the authors analyzed postoperative phosphorus levels in 719 patients after major hepatectomy [18]. In this large study, the authors reported that phosphorus levels >2.4 mg/dl and a delayed nadir beyond postoperative day 3 are strong predictors of postoperative liver insufficiency, major complications, and early mortality.

Postoperative Abdominal Drainage

There is still debate on the use of routine prophylactic abdominal drainage after liver resection, as it may be possibly harmful and uncomfortable for the patients. One of the landmark studies with the strongest evidence to omit drainage after abdominal surgery arises from a meta-analysis published in 2004 [19]. This meta-analysis, however, included three randomized controlled trials (RCTs) on liver resection only, with low sample sizes [20, 21]. More recently, a reappraisal of prophylactic drainage in uncomplicated liver resections was performed in a meta-analysis [22]. Six RCTs with 665 patients were included in the quantitative analysis. The incidence of ascitic leak was higher in the drained group. The rate of surgical site infections, wound infections, chest infections, biliary fistula, length of stay, and mortality was not different between patients with or without prophylactic drainage. Within an enhanced recovery program, Wong-Lun-Hing et al. showed that resection surface-related morbidity, mortality, and re-intervention rates after liver surgery without prophylactic drainage were comparable with standard care [23]. A no-drain policy after hepatectomy within an ERAS protocol can be implemented safely. By the time of the editing of the ERAS recommendations for liver surgery, the available evidence was nonconclusive, and no recommendation was given for the use of prophylactic drainage or against it after hepatectomy. There is now accumulating evidence to avoid prophylactic abdominal drainage after liver surgery in non-cirrhotic patients.

Minimally Invasive Approach

The minimally invasive approach is one of the key elements of an enhanced recovery after surgery program. The second international consensus conference on laparoscopic liver resection in Morioka 2014 (Japan) highlighted that minor laparoscopic liver resection (LLR) has become standard practice, while major LLR still remains an innovative procedure and deserves further investigations [24]. More recently, the Southampton Consensus Guidelines for Laparoscopic Liver Surgery was held in 2017, with the specific aim of presenting and validating guidelines for LLR [25]. The conclusions of these two consensus conferences showed that a laparoscopic approach appears to reduce postoperative complications and postoperative stay compared to open procedures. Laparoscopic liver resection lowers the incidence of postoperative ileus. In addition, patients have faster oral intake and require less intravenous narcotic use [26–28]. Preliminary results of the first large-scale prospective RCT comparing laparoscopic and open surgery for colorectal liver metastases (COMET study) have shown improved short-term outcomes for the LLR approach, which is supported by previous propensity score-matched studies [29]. In cirrhotic patients with hepatocellular carcinoma (HCC), a laparoscopic approach appears to reduce the incidence of postoperative ascites, liver failure, and morbidity with no difference in overall or disease-free survival at 2 years compared to open procedures [30, 31]. For major hepatectomies, the largest meta-analysis has shown that the laparoscopic approach has less blood loss, morbidity, and length of stay with similar operative times, transfusion rates, and completeness of resection compared with the open approach [32]. Similar results were demonstrated for left hemi-hepatectomies [33, 34]. For minor resections, mainly left lateral resection and resections of lesions located in anterior segments (IVb, V), the laparoscopic approach should become the gold standard. Laparoscopic left lateral sectionectomies are consistently associated with shorter hospital stay when compared with the open approach [35]. However, the results of the ORANGE II trial, which compared open versus laparoscopic left lateral hepatic sectionectomy within an ERAS program, failed to show a faster functional recovery with the laparoscopic approach and had to be stopped prematurely due to slow accrual [23].

In a meta-analysis by Yang et al. comparing ERAS programs with traditional care in laparoscopic liver resection (8 studies, 580 patients), the authors concluded that ERAS in laparoscopic liver surgery accelerates the postoperative recovery and is cost-effective [36]. Compared with traditional care, ERAS was associated with significantly accelerated time to first diet after surgery, time to flatus, and grade I-II complications according to Dindo-Clavien complications. Hospital stay was shortened, and hospital cost reduced in the ERAS group.

To date, there are no studies assessing the safety of robotic liver surgery in patients within an ERAS program. Robotic liver resection seems to be feasible by hepatobiliary surgeons with advanced training, especially for lesions located in the posterosuperior segments [37, 38]. However, according to a recent large series comparing robotic versus laparoscopic liver resections, significant benefits were not demonstrated yet [39]. In addition, as stated in the Southampton Consensus, the robotic approach has a longer operative time and higher costs compared with the laparoscopic approach. Blood loss, length of stay, resection margins, and morbidity seem to be similar [37, 40].

Postoperative Glycemic Control

Perioperative hyperglycemia is frequently observed after major surgery [41, 42]. These changes result mainly from the combination of the surgical stress with a transient insulin resistance with a compromise peripheral insulin-dependent glucose uptake [43]. Hyperglycemia results in deregulation of liver metabolism and immune function, impairing postoperative recovery. Postoperative insulin sensitivity is significantly reduced in patients not treated with insulin during surgery [44]. In addition, there is a rapid change in glucose concentration during hepatectomy with Pringle maneuver, reflecting glycogen breakdown within hepatocytes secondary to hypoxia [45]. Only a few studies have evaluated the effect of perioperative hyperglycemia, mainly focusing on the extent of hepatic injury. In 85 patients, Han et al. evaluated whether intraoperative hyperglycemia during liver resection is associated with the extent of hepatic injury [46]. Blood glucose concentrations were measured at predetermined time points including every end or start of Pringle maneuver via arterial blood analysis. Thirty-five percent of the patients developed hyperglycemia (blood glucose > 180 mg/dl) during surgery. Prolonged Pringle maneuver, cirrhosis, lower prothrombin time, and greater total cholesterol level were determined as risk factors for hyperglycemia. In addition, hyperglycemia was independently associated with the extent of liver injury.

There is evidence that preoperative oral supplementation with carbohydrate and branched-chain amino acid-enriched nutrient decreased insulin resistance in patients undergoing hepatectomy [47]. A systematic review included 17 randomized trials with 1445 surgical patients showed that patients receiving carbohydrates had less insulin resistance and fewer symptoms such as malaise, hunger, thirst, nausea, or anxiety [48]. No difference in terms of complications was observed.

Finally, a raised blood lactate after liver surgery, which correlates with postoperative morbidity, can be related to insulin resistance or to a mix between insulin resistance and ischemia-reperfusion injury [49]. In the study by Vibert et al., diabetes was the only preoperative predictor of increased lactate level after liver surgery [49]. Diabetes is associated with impaired lactate metabolism via gluconeogenesis. In addition, diabetes may have an impact on liver damage following inflow occlusion in patients with nonalcoholic steatohepatitis undergoing liver resection [50]. Therefore, insulin therapy is recommended and should be initiated early during liver surgery to maintain normoglycemia between 80 and 120 mg/dL. Programmed infusion of insulin administered as determined by the control algorithm of a closed-loop artificial endocrine system (i.e., an artificial pancreas) should be preferred to manual injection of insulin according to the commonly used sliding scale [51].

Postoperative Nutrition and Early Oral Intake

It is well-known that early enteral feeding prevents gastrointestinal (GI) atrophy, maintains immunocompetence, and preserves the normal gut flora when compared to total parenteral nutrition (TPN). Patients who require liver resection due to malignancy often suffer from mild-to-severe malnutrition, making them more susceptible to disturbed metabolic homeostasis. A first systematic review published in 2006, including 5 RCTs, showed that early enteral nutrition after liver resection decreased the incidence of postoperative complications compared to parenteral nutrition [52]. Subsequently, Lassen et al. underwent a randomized multicenter trial aiming to investigate whether the routine use of normal food at will increases morbidity after major upper gastrointestinal surgery. Patients (66 underwent liver resection) were randomly assigned to a routine of nil-by-mouth and enteral tube feeding by needle catheter jejunostomy or normal food at will from the first day after major upper GI surgery. There was no difference in complications, reoperations, or mortality, but resumption of bowel function was faster in the early food group [53]. More recently, Hendry et al. demonstrated the benefits of the routine use of oral laxatives combined with oral nutritional supplements in liver surgery patients within an enhanced recovery pathway, which resulted in an earlier first passage of stool, but the overall rate of recovery was unaltered [54]. According to the European Society for Clinical Nutrition and Metabolism (ESPEN) and American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines, postoperative supplemental nutrition is only indicated in malnourished patients or in prolonged postoperative fasting (>5 days) such as when severe complications arise [55–57]. It is noteworthy that most studies suffer from insufficient patient volume as well as heterogeneity of the patient populations and nutritional protocols. More randomized trials are needed to corroborate those findings.

Postoperative Nasogastric Intubation

The dogma of the routine use of nasogastric tube (NGT) decompression after abdominal surgery has been recently questioned. Two Cochrane systematic reviews demonstrated that prophylactic nasogastric intubation after abdominal surgery should be abandoned in favor of selective use. Increased pulmonary complications and longer time to return of bowel function were observed in patients with routine nasogastric tube [58]. The first large RCT in liver surgery by Pessaux et al. (n = 200 patients) confirmed that routine NGT decompression after elective hepatic resection had no advantage [59]. Its use was associated with increased risk of pulmonary complications (mainly pneumonia). More recently, another RCT by Ichida et al. (n = 210 patients) demonstrated that there are no differences between the NGT and no-NGT groups in terms of the overall morbidity, incidence of pulmonary complications, frequency of postoperative vomiting, time to first oral intake, or postoperative duration of hospital stay [60]. The routine use of NGT decompression in patients undergoing elective liver surgery does not appear to be advantageous; moreover, it causes significant patient discomfort during the postoperative period and should be then avoided. For this item, the level of evidence is high, and it has a strong grade of recommendation [10].

Analgesia

Thoracic epidural analgesia (TEA) is the standard analgesic technique in patients undergoing various types of major surgery. The main benefits of this technique are pain control, early mobility, improved cardiopulmonary function, decreased gastrointestinal symptoms, and reduced risk of thromboembolism [61–63]. According to the ERAS guidelines, the routine use of TEA cannot be recommended in open liver surgery since one recent RCT comparing the role of local anesthetic wound infusion catheter plus patient-controlled opiate analgesia to standard TEA failed to show a superiority of TEA. Wound infusion reduced the length of time required to fulfill criteria for hospital discharge [64]. On the other hand, a meta-analysis including 4 RCTs (n = 705 patients) has shown lower pain scores on postoperative day 1 with epidural but similar outcome compared to local anesthetic infiltration via wound catheters [65].

A concern using TEA is the possible prolongation of prothrombin time after hepatectomy, which may delay epidural

catheter removal and increase administration of corrective blood products [66]. In addition, 10–16% of patients undergoing liver resection develop acute kidney injury (AKI) [67]. To reduce intraoperative bleeding during parenchymal transection, liver resections are performed with usually low CVP, mainly by perioperative restriction. TEA-associated arterial hypotension commonly occurs because of sympathicolysis and subsequent peripheral vasodilatation. Combining low CVP with TEA-associated hypotension may lower the mean arterial pressure even further, which may compromise renal blood flow leading to acute kidney injury. Kambakamba et al. have addressed this particular issue in a large study including 1153 patients [68]. The authors found that 8% of patients developed acute kidney injury after open liver resection with an increased morbidity and mortality compared to patients with no kidney failure. The incidence of AKI was significantly higher in the TEA group, particularly after major hepatectomy, and TEA remained an independent risk factor for AKI in multivariate analysis.

Conclusion

The value of enhanced recovery pathways has now been demonstrated in colorectal surgery; however, there is a need to perform more high-quality studies to confirm the benefit of ERAS in liver surgery. According to the ERAS liver group recommendations, 16 out of the 23 standard items of ERAS were studied for liver surgery; however, the quality and level of evidence of the studies remain low (Table 56.1) [10]. The highest level of evidence (level 1 or 2) was available for only five items. We have now at least two meta-analyses confirming that ERAS is a safe and effective program in liver surgery. Compared to standard care, ERAS program reduces the length of hospital stay and favors earlier bowel movement. Of note, discharged criteria vary among studies. Intraoperative and postoperative balanced fluid control is a key issue in liver surgery and should be monitored closely to prevent fluid overload and weight gain, which are two factors strongly associated with postoperative complications and prolonged hospital stay. One situation in liver surgery that requires particular attention is the presence of cirrhosis. This situation may affect significantly the recovery progress after hepatectomy. To date, only one study comparing the ERAS program to traditional care in laparoscopic hepatectomy compared preoperative liver function or cirrhosis level [69]. This situation specific to liver surgery needs to be addressed in future trials on ERAS. Finally, compliance with the new proposed liver ERAS protocol should be documented as part of further trial to allow benchmarking.

Table 56.1 Summary of ERAS recommendations for each item and the respective level of evidence

ERAS items	Summary	Evidence level	Grade of recommendation
1. Preoperative counseling	Patients should receive routine dedicated preoperative counseling and education before liver surgery	Moderate	Strong
2. Perioperative nutrition	Patients at risk (weight loss > 10–15% within 6 months, BMI < 18.5 kg/m2, and serum albumin < 30 g/l in the absence of liver or renal dysfunction) should receive oral nutritional supplements for 7 days prior to surgery. For severely malnourished patients (>10% WL), surgery should be postponed for at least 2 weeks to improve nutritional status and allow patients to gain weight	High	Strong
3. Perioperative oral immunonutrition	There is limited evidence for the use of IN in liver surgery	Low	Weak
4. Preoperative fasting and preoperative carbohydrates load	Preoperative fasting does not need to exceed 6 hours for solids and 2 hours for liquids. Carbohydrate loading is recommended the evening before liver surgery and 2 hours before induction of anesthesia	No preoperative fasting more than 6 hours: moderate Carbohydrate loading: low	No preoperative fasting more than 6 hours: strong Carbohydrate loading: weak
5. Oral bowel preparation	Oral MBP is not indicated before liver surgery	Low	Weak
6. Pre-anesthetic medication	Long-acting anxiolytic drugs should be avoided. Short-acting anxiolytics may be used to perform regional analgesia prior to the induction of anesthesia	Moderate	Strong
7. Antithrombotic prophylaxis	LMWH or unfragmented heparin reduces the risk of thromboembolic complications and should be started 2–12 hours before surgery, particularly in major hepatectomy. Intermittent pneumatic compression stockings should be added to further decrease this risk	Use of heparin: moderate Use of intermittent pneumatic compression devices: low	Use of heparin: strong Use of intermittent pneumatic compression devices: weak

Table 56.1 (continued)

ERAS items	Summary	Evidence level	Grade of recommendation
8. Perioperative steroids administration	Steroids (methylprednisolone) may be used before hepatectomy in normal liver parenchyma, since it decreases liver injury and intraoperative stress, without increasing the risk of complications. Steroids should not be given in diabetic patients	Moderate	Weak
9. Antimicrobial prophylaxis and skin preparation	Single-dose intravenous antibiotics should be administered before skin incision and less than 1 hour before hepatectomy. Postoperative "prophylactic" antibiotics are not recommended Skin preparation with chlorhexidine 2% is superior to povidone-iodine solution	Antimicrobial prophylaxis: moderate Skin preparation: moderate	Antimicrobial prophylaxis: strong Skin preparation: strong
10. Incision	The choice of incision is at the surgeon's discretion. It depends on the patient's abdominal shape and location in the liver of the lesion to be resected. Mercedes-type incision should be avoided due to higher incisional hernia risk	Moderate	Strong
11. Minimally invasive approach	LLR can be performed by hepatobiliary surgeons experienced in laparoscopic surgery, in particular left lateral sectionectomy and resections of lesions located in anterior segments There is currently no proven advantage of robotic liver resection in ERAS. Its use should be reserved for clinical trials	Minimally invasive approach: moderate Robotic surgery: low	Minimally invasive approach: strong Robotic surgery: weak
12. Prophylactic nasogastric intubation	Prophylactic nasogastric intubation increases the risk of pulmonary complications after hepatectomy. Its routine use is not indicated	High	Strong
13. Prophylactic abdominal drainage	The available evidence is nonconclusive, and no recommendation can be given for the use of prophylactic drainage or against it after hepatectomy	Low	Weak
14. Preventing intraoperative hypothermia	Perioperative normothermia should be maintained during liver resection	Moderate	Strong
15. Postoperative nutrition and early oral intake	Most patients can eat normal food at day 1 after liver surgery. Postoperative enteral or parenteral feeding should be reserved for malnourished patients or those with prolonged fasting due to complications (e.g., ileus >5 days, delayed gastric emptying)	Early oral intake: moderate Oral nutritional supplements: moderate No routine postoperative artificial nutrition: high	Early oral intake: strong Oral nutritional supplements: weak No routine postoperative artificial nutrition: strong
16. Postoperative glycemic control	Insulin therapy to maintain normoglycemia is recommended	Moderate	Strong
17. Prevention of delayed gastric emptying (DGE)	An omentum flap to cover the cut surface of the liver reduces the risk of DGE after left-sided hepatectomy	High	Strong
18. Stimulation of bowel movement	Stimulation of bowel movement after liver surgery is not indicated	High	Strong
19. Early mobilization	Early mobilization after hepatectomy should be encouraged from the morning after the operation until hospital discharge	Low	Weak
20. Analgesia	Routine TEA cannot be recommended in open liver surgery for ERAS patients. Wound infusion catheter or intrathecal opiates can be good alternatives combined with multimodal analgesia	Moderate	Strong
21. Preventing postoperative nausea and vomiting (PONV)	Multimodal approach to PONV should be used. Patients should receive PONV prophylaxis with two antiemetic drugs	Moderate	Strong
22. Fluid management	The maintenance of low CVP (below 5 cmH2O) with close monitoring during hepatic surgery is advocated. Balanced crystalloid should be preferred over 0.9% saline or colloids to maintain intravascular volume and avoid hyperchloremic acidosis or renal dysfunction, respectively	Moderate	Strong
23. Audit	Systematic audit improves compliance and clinical outcome in healthcare practice	Moderate	Strong

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BMI body mass index, *WL* weight loss, *IN* immunonutrition, *MBP* mechanical bowel preparation, *LMWH* low-molecular-weight heparin, *LLR* laparoscopic liver resection, *TEA* thoracic epidural analgesia, *CVP* central venous pressure

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Pancreatic Surgery

57

Linn S. Nymo and Kristoffer Lassen

Introduction

Pancreatic Surgery in the Age of ERAS

Elective pancreatic surgery can be one of two types: a pancreatoduodenectomy (PD, Whipple's resection) or a distal pancreatic resection (DP, left-sided, subtotal, or tail resection). Apart from the fact that both are pancreatic resections, the two procedures have little in common. PDs are complex procedures resulting in at least three anastomoses and a resection also of the duodenum. DPs result in a cut end of the left part of the gland, but no anastomosis and no intestinal resection.

From the first years of enhanced recovery after surgery (ERAS), the main challenge for dissemination of modern protocols was the reluctance to stop using the nasogastric decompression tube and to allow food at will. This affected ERAS development in pancreatic surgery, and the PDs practice has for almost two decades been a "pocket of resistance" to ERAS development. Even well into the present decade, this procedure was associated with a high rate of major complications and perioperative mortality [1], a situation that spurred a marked conservatism.

The situation is now different. Modern results are improving with mortality after PD dropped below 3% in high-volume centers [2] and rates of reoperations are below 15%. The DPs are to an increasing degree performed laparoscopically with a marked impact on length of stay [3]. Modern interventional radiology offering image-guided percutaneous drainage of postoperative accumulations have lowered morbidity and reduced the need for reoperations and the use of prophylactic wound drains. The first set of ERAS® Society comprehensive consensus guidelines for pancreatoduodenectomies were published simultaneously in two separate journals in 2012 [4, 5]. The overall summary of these guidelines is presented in Table 57.1. Many of the recommendations are generic for most major abdominal procedures and will not be covered in this chapter. Instead, the elements that are specific and/or may differ from most other guidelines will be discussed. A revised version of the 2012 guidelines is expected to be published in 2020.

Meta-analyses have concluded that ERAS protocols reduce length of stay following pancreatic surgery [6], and non-randomized data also suggest that complication rates are reduced [7–9]. It should be noted, however, that benefits of ERAS protocols are hard to assess in an unbiased manner. ERAS protocols are complex interventions with no obvious control group, plagued by cross-contaminations, and not well suited for a randomized trial [10]. As an updated ERAS protocol will always represent best available knowledge, it is not easy (or ethically sound) to perform a direct comparison with other routines. The jury is still out regarding whether the provision of any protocol might well be the pivotal intervention, rather than any specific protocol contents [11]. That said, there appears to be a clear *association* between better outcomes and higher adherence to the ERAS protocol items for colorectal surgery [12, 13], and a causal relationship could well be suspected.

Many patients will fare well and land safely even without any dedicated perioperative protocol. Many of these patients have the benefits of being fit at the outset and undergoing surgery of limited magnitude. This implies that they have wide safety margins and may be able to cope reasonably well even if additional burdens are stacked on them during their stay. A pancreatoduodenectomy is a major undertake and in a frail and comorbid elderly patient can be challenging, and one where attention must be paid to every detail to optimize the perioperative journey.

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Table 57.1 ERAS recommendations for pancreatic surgery

Topic	Recommendations	Level	Grade
Preoperative nutrition	Patients should be screened for weight loss preoperatively	Moderate	Strong
	Artificial nutritional intervention is not recommended in the absence of severe malnutrition	Moderate	Moderate
	Immunonutrition is not recommended	Strong	Strong
Obstructive jaundice and preoperative biliary drainage	Routine drainage in uncomplicated jaundice should be avoided for patients otherwise eligible for up-front surgery	Strong	Strong
	When drainage is indicated, covered metallic stents are preferred	Moderate	Moderate
Minimally invasive techniques (MIT)	Advisable for DP	Moderate/strong	Strong
	Implementation of MIT for PD should only be done within trial or registry settings	Moderate	Strong
Prophylactic intra-abdominal drainage	Routine omission is not recommended. A risk-stratified approach is advised	Moderate/strong	Strong
Nasogastric drainage (NGD)	Routine NGD is not necessary and can be placed on demand	Moderate	Strong
Postoperative diet	Oral drinks and food at will from the first day after surgery are recommended. Supplements of intravenous fluids should be administered on demand. Sip feeds may enhance the caloric and protein intake	Strong	Strong

DP distal pancreatic resection, *PD* pancreatoduodenectomy

Measuring Outcome and Methodological Challenges

Functional recovery is rated very highly by patients and professionals [14], but not easy to monitor. Hard endpoints, such as reoperations and mortality, are important but luckily only apply to a minority. Length of stay (LoS) has been criticized for not necessarily reflecting functional recovery, but it is easy to measure and reflect the use of health services to some degree. When LoS is lower than anticipated and transfer stays and readmissions are included, it is probably not a poor reflection of the patients' clinical and functional recovery. If transfer and readmission stays are added to the index stay, this may be analyzed as an "aggregated length of stay" or a-LoS [3]. For a large Norwegian cohort of pancreatic surgery patients, this yielded a median a-LoS of 14 days for PD patients, 13 days for open distal resections, and 7 days for laparoscopic distal resections [15, 16].

The use of R0/R1 resection ratio (microscopic radicality) as a surrogate endpoint for oncological outcome [17] is challenged by the redefined examination routines for pancreatic specimens that have seen R1 rates soar to a level where this now applies to the majority of cases [18–20]. Randomized comparison of laparoscopic and open access are further complicated by the skill-dependent nature of these interventions and a marked learning curve, and these features challenge internal and external validity of trial results [10].

Preoperative Nutrition

The prognostic significance of weight loss preceding major surgery has been recognized since the 1930s [21]. It is important to recognize that body mass index (BMI) in itself is a poor marker of malnutrition in pancreatic cancer patients, as obese patients often have suffered a greater weight loss and are more malnourished than slender patients [22]. Using premorbid self-reported weight and scaling before surgery, as little as 5% weight loss has been shown to be significantly associated with an increased rate of complications [23]. Not surprisingly, this has spurred a desire to intervene with artificial nutrition in an attempt to restore nutritional status before high-risk operations. Nutritional interventions (parenterally, enterally, or orally by sip feeds) have been widely advocated in patients with significant weight loss heading for major surgery [24, 25], and they usually result in increased weight. Whether this weight gain has any impact on the risk for complications is another issue. Importantly, level-A evidence (blinded and randomized trials with relevant control groups) showing benefits on meaningful clinical outcomes are very few and mostly outdated. Bearing in mind that this is an intervention that is well suited for examination by a double-blinded randomized controlled trial (RCT) (the intervention is stable and not skill dependent; i.e., has no learning curve [10]), we should accept nothing short of this level of evidence. The topic applies to pancreatic surgery in particular, as the majority of patients with a pancreatic malignancy have suffered a significant weight loss before they reach surgery [26]. To date, it is not proven that preoperative nutritional support reduces complication rates or enhances recovery for pancreatic resections or for any other formal gastrointestinal resections for that matter. Interestingly, and importantly, a recent evaluation of a series of established screening tools for malnutrition showed that none of them had any prognostic ability for pancreatic surgery patients [27], hence suggesting that preoperative weight loss based on patient-reported premorbid weight is sufficient for screening.

It is probably prudent to provide nutritional support to patients who suffer severe malnutrition; i.e., more than a 15% weight loss or having a disease-caused BMI drop to <18.5 kg/m^2 [28]. It may improve their well-being, and one

must keep in mind that patients in extreme situations are not covered by data from available trials from which these groups would normally be excluded. For those with a moderate degree of weight loss, nutrition support preoperatively is recommended by the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines of 2006 and 2017, but this is primarily deduced from uncontrolled or unblinded trials or focusing on surrogate outcomes [24, 25]. Of the 35 controlled trials forming the database for the most recent ESPEN recommendation [25], none were published later than 2004. These ESPEN guidelines also recommended the provision of immune-enhancing components (glutamine and arginine) to prevent infectious complications [24, 25]. Of a large number of studies reporting a benefit of immunonutrition, only a small minority are double-blinded, have an isonitrogenous control group, and are powered for relevant clinical outcomes. High-quality trials from the latest decade recruiting high-risk patients have not demonstrated any benefit from immunonutrition [29–31], and this was confirmed by a recent meta-analysis [32]. Double-blinded RCTs in pancreatic resection patients are lacking and, based on extrapolations from the current evidence pool, should not be attempted until we have other agents to evaluate. The ERAS guidelines for pancreatic surgery do not recommend artificial nutritional intervention in patients not suffering severe malnutrition, and they do not recommend the use of immunonutrition at all [4, 5].

Obstructive Jaundice and Preoperative Biliary Drainage

The proposed negative physiological impact from jaundice includes coagulopathy, impairment of renal and cardiac function, and susceptibility to hypotension [33]. From an ERAS perspective, these are all intuitive subjects to address. Traditionally, jaundiced patients have undergone preoperative biliary drainage aiming to prevent acute obstructive cholangitis, relieve itching, and reduce postoperative complications. However, the negative physiological effects of otherwise uncomplicated jaundice over a limited time period are not well documented and probably not large enough to justify routine drainage for all [34]. Percutaneous transhepatic drainage (PTC) and Endoscopic retrograde Cholangio-Pancreatography (ERCP) stenting both have potentially devastating complications such as hemorrhage, perforation, cholangitis, and pancreatitis that can delay or even preclude further oncological or surgical treatment. Further, preoperative biliary drainage contaminates and changes the biliary microbiome toward a more pathogen-prone spectrum that can lead to higher rates of postoperative infectious complications [35–37]. For patients with obstructive jaundice scheduled for pancreatoduodenectomy, there is now a reasonable amount of evidence suggesting that routine preoperative biliary drainage, in contradiction to earlier paradigms, leads to a higher overall risk of complications, both related to the drainage procedure and the pancreatic resection [38–41]. The evidence mainly stems from one Dutch RCT [38], but also several recent meta-analyses support a selective approach to preoperative drainage. It is fair to conclude that routine preoperative biliary drainage should be avoided in patients otherwise eligible for up-front pancreatic resection, even if they are severely jaundiced. If organizational constraints alone preclude direct surgery within a week or two for jaundiced patients, these issues need to be addressed instead.

In case of cholangitis or severe symptomatic jaundice in patients where surgery for some reason has to be delayed, preoperative drainage will still be indicated. The increasing use of neoadjuvant chemotherapy regimens for pancreatic cancer with subsequent need of biliary drainage further underlines the call for evidence regarding the optimal drainage technique. In eligible patients, endoscopic retrograde stenting has traditionally been the preferred method over percutaneous transhepatic drainage due to high success rates, no external drain, and a perception of a lower complication burden [42]. However, the superiority of ERCP compared to modern PTC techniques is being challenged [43], and they could probably be considered reasonably equal today. This implies that one may adjust strategy to fit with local availability of the one or the other. Self-expanding, fully covered metallic stents should probably be preferred over plastic stents due to lower risk of stent-related complications and superior patency [44–47].

Minimally Invasive Techniques in Pancreatic Resection

Minimally invasive (MI) techniques—either conventional laparoscopy, robot-assisted laparoscopy, or hybrid techniques are evolving in both pancreatoduodenectomy (PD) and distal pancreatic resection (DP). They have gained popularity in the last decade, and indications are currently expanding. Both short-term (surgical) and long-term (oncological) outcomes must be considered when assessing these methods.

Minimally invasive techniques (mostly totally laparoscopic) are widely established for DP [48], including for malignant tumors [49]. No published RCTs exist to date, but two are underway (the Dutch LEOPARD-1 [50] and the Swedish LAPOP trial). Numerous registry-based studies, cohort series, and systematic reviews have shown equal or superior short-term outcomes after minimally invasive DP

[17, 49, 51–54]. MI techniques for DP hold the same advantages for the patients as all other MI surgery in terms of faster recovery without need for epidural analgesia and shorter LoS. MI technique for distal pancreatectomy is a valid and recommendable option in experienced hands.

For PDs, the landscape is significantly more blurred. Technically, an open PD is considered a complex major procedure and a Minimally Invasive PancreatoDuodenectomy (MIPD) even more so. Limited MIPD series from expert centers, including surgery for PDAC or with major vascular reconstruction, are currently reported with promising results [55, 56]. However, benefits from MI techniques for PD beyond a marginally faster recovery are yet to be proved. One single-institution RCT [57] and several register-based larger cohort studies have shown comparable overall outcomes compared to open PD but higher postoperative pancreatic fistula (POPF) rates after MIPD and higher mortality after MIPD in low-volume centers [57–66]. A recent multicenter RCT (LEOPARD-2) comparing laparoscopic and open PD included a pre-study training program but was prematurely terminated due to excess mortality in the MIPD arm and did not show superior results for MIPD with regard to functional recovery [67]. So far the promising results from selected patient series in dedicated high-volume centers have not been reproducible on a larger scale. The available data suggest that substantial benefits from MI techniques for PD remain to be proven and that further exploration should be done only within trial or registry settings with comprehensive education programs and in high-volume centers.

Prophylactic Intra-abdominal Drainage

Prophylactic drainage of the resection field has historically been considered standard of care for all pancreatic resections. The major rationale has been to evacuate accumulated fluids such as pancreatic juice, bile, blood, and chyle and subsequently avoid infection. In addition, drains have been thought to contribute to early and preferably preclinical identification of pancreatic or biliary leaks and consequently serve as a basis of preventive management strategies and timely intervention. For distal resections, the formation of a pancreatic fistula is almost the only feared major complication and a common cause of prolonged hospital stay and readmission. A drain that produces large volumes of amylase-rich content is obviously a well-working contraption. A dry drain, however, means either that the patient is doing well or that the drain is doing badly. The distinction is frequently difficult to make. In the past decades, routine use of prophylactic drains has been challenged. The opponents point to the risk of retrograde infection and for PD that closed suction drains constitute an unnecessary mechanical stress to the anastomosis, which itself may contribute to leak and fistula formation. In addition, postoperative drains limit patient mobilization and hence violate an ERAS pillar to optimal postoperative surgical care. Due to advances in invasive radiology, pancreatic centers now have access to percutaneous drainage of accumulations demonstrated on imaging, and this has influenced the debate.

The literature covering this field reaches diverging conclusions. One RCT (PANDRA trial) allocated patients to drainage or no drainage intraoperatively during PD without risk stratification and concluded on inferior outcomes after prophylactic drains [68]. However, this trial has been criticized for a high trial-violation rate (drains placed at surgeons' discretion when randomized to no drain), and only 13% of patients were found eligible for inclusion. Both issues raise concerns for the generalizability of the results. Another RCT using a similar methodology but with a lower rate of protocol violations was halted prematurely due to excess mortality in the no-drain group and concluded that the routine abandoning of drains increased morbidity and mortality [69]. None of these two trials used a risk-stratified approach to the question of drainage, which is probably more feasible. A multicenter prospective cohort study from McMillan et al. comparing patient cohorts before and after implementing a selective drainage protocol based on the fistula risk score (duct size, gland texture, pathology, and intraoperative hemorrhage [70]) showed that drains can be safely omitted in one out of four PDs [2]. This selective approach has been supported in other retrospective cohort series [71, 72] and further confirmed in several meta-analyses and systematic reviews covering both PD and distal pancreatectomy (DP) [73–78].

Whenever a drain is placed, the timing of drain removal remains in question. An RCT addressing the optimal timing supported early removal at postoperative day 3 for low-risk patients [79]. Early drain removal in low-risk resections, defined by low concentration of amylase value in drain fluids, is supported by several meta-analyses [73, 75, 80].

In conclusion, avoidance of prophylactic drainage of *low-risk* pancreatic resections is probably safe, but whether a short-duration drain is actually detrimental is unclear. Conversely, the application of routine drainage after *high-risk* pancreatic resections is recommended. A selective, risk-stratified approach seems appropriate. Early drain removal in low-risk patients is recommended.

Nasogastric Drainage

The nasogastric (NG) tube and a nil-by-mouth regimen were hallmarks of traditional postoperative care in abdominal surgery for more than a century. While now mostly abolished as a routine measure, it lingers in some fields of major resections with high-risk anastomoses, like those constructed after pancreatic head resections. PD patients could undergo regimens with nil-by-mouth for days or weeks

postoperatively [81]. In PDs, delayed gastric emptying (DGE) [82] is relatively common (10–30%), and this probably also explains the traditional preference for prophylactic NG decompression by many surgeons. Over the last decade, there has been an increasing recognition that an NG is not routinely required and that the problem of DGE has been exaggerated [4]. While high-powered trials are not available, modern meta-analyses and systematic reviews in PD patients do not routinely recommend routine use of postoperative NG tubes and suggest instead a selective approach on demand [4, 83, 84]. In a Norwegian single-center cohort of 201 PD patients that left the theater without an NG tube, 182 had a postoperative course without need for re-laparotomy, and 26 (14%) of these had an NG tube reinserted on demand [85].

Postoperative Diet and Artificial Nutrition

It is important to acknowledge that there is a vital distinction between some terms that have been mixed up in earlier trials [86]. Enteral nutrition denotes an artificial way of feeding by tube or catheter to the stomach or proximal small bowel. This modality bypasses physiological reflexes, as is also the case with parenteral nutrition. Both have important roles in complicated cases, but should not be used routinely in modern protocols. Eating a normal diet is not a mode of enteral nutrition but something vastly more important. Eating and drinking is the optimal way of providing fluids and nutrients but also a process that is volitional and physiological and one that integrates all the physiological reflexes that enhance digestion and well-being. Removing the routine use of NG tubes from care bundles (see above) created the possibility for allowing patients to drink and eat a normal diet from the first day after surgery. The safety and the advantages of this strategy are corroborated by meta-analyzed data and cohort series [83, 84] and advocated by modern recommendations [4]. One must, however, remember that gut function is often reduced in the first few days after a PD. A modern and evidence-based strategy is to offer the PD patients normal food at will from the first postoperative day but at the same time informing them to begin carefully and to increase according to tolerance [4, 83, 87]. The caloric or protein intake may not necessarily be substantial in the first 3–4 days, but this must be viewed against the acknowledged risks of artificial tube feeding [84]. Offering sip feeds of oral nutritional supplements may increase the intake of energy and protein postoperatively, but improved outcomes have not been documented. Artificial nutrition by enteral or parenteral catheter should only be used selectively in patients who suffer major complications and cannot eat normally and in the (few) patients with long-standing gastric retention resistant to repeated attempts at normal food and temporary drainage. For these few, an enteral route has

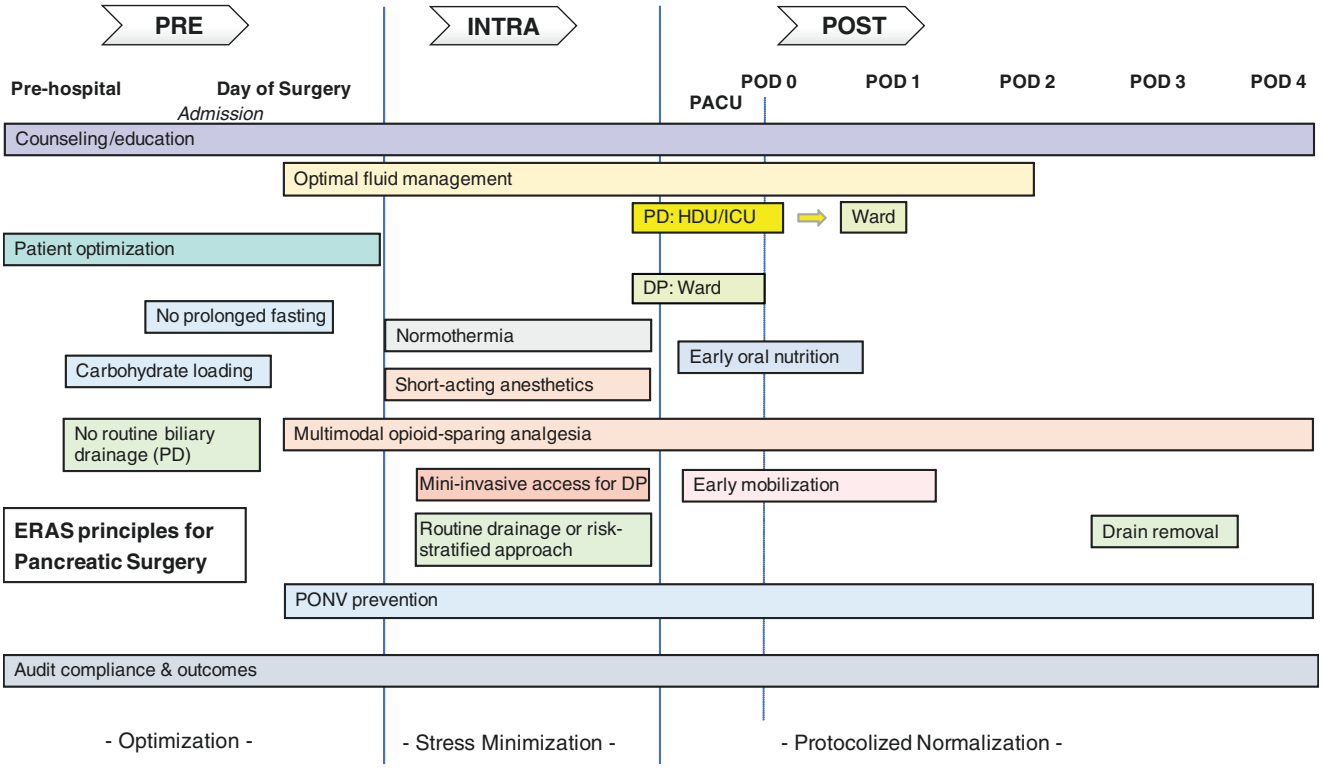

Fig. 57.1 ERAS principles for pancreatic surgery. PACU, postanesthesia care unit; POD, postoperative day; PD, pancreatoduodenectomy; HDU, high-dependency unit; ICU, intensive care unit; DP, distal pancreatic resection; PONV, postoperative nausea and vomiting

traditionally been advocated, but most of the data stem from outdated protocols [88].

Conclusion

Modern enhanced recovery pathways should be implemented as standard of care for all major resections—including pancreatoduodenectomies (Fig. 57.1). The avoidance of routine preoperative biliary drainage, allowing early normal food at will, and placing postoperative nasogastric drainage only on demand are the most important aspects.

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Pediatric Enhanced Recovery After Surgery

58

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Introduction

The enhanced recovery after surgery (ERAS) care model has played a significant role in improving surgical care and patient recovery over the past 20 years. First introduced as fast track to the international perioperative community by Dr. Henrik Kehlet in the 1990s, the further development of the concept of ERAS has been a positive disruptor of traditional surgical care of adult patients in most developed countries, with growing influence in low- to middle-income countries [1]. As noted in other chapters throughout this textbook, ERAS is a patient-centered strategy that encompasses the full spectrum of perioperative care, seeking to optimize the surgical experience of the patient by consistently providing high quality, safe, and efficient care. These aims are achieved with thoughtful multidisciplinary planning and a focus on preoperative, intraoperative, and postoperative optimization. Guidelines generated from the ERAS® Society as well as multiple clinical trials in adults have shown benefit in colorectal surgery, general surgery, cardiac surgery, gynecologic surgery, orthopedic surgery, and otolaryngology surgery. ERAS pathways have been shown to confer quantitative benefits in multiple perioperative metrics such as hospital length of stay (LOS), opioid consumption, opioid-related adverse events, time to enteral feeding, and early postsurgical mobility.

Enhanced recovery after surgery is still in its infancy in the pediatric surgical specialties. The first pediatric ERAS protocols were reported in 2009 by Ure et al., who reported that pediatric ERAS was safe and effective for more than 70% of their scope of general surgery and urologic practice in children [2–4]. Parental satisfaction with ERAS was high, and postsurgical LOS was decreased as the children safely met their discharge goals earlier in the recovery period [5]. This initial experience was followed by Mattei et al. in a focused experience, labeled "fast track," for patients with Crohn's disease undergoing ileocecal resections [6]. As pediatric ERAS became more widely utilized from 2010 to 2019, it was apparent that organization of like-minded individuals focused on application of ERAS principles to children was required. The first World Congress for Pediatric ERAS® was held in Richmond, Virginia, in 2018 with the specific aim of

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organizing a collaborative workgroup of international experts interested in improving pediatric perioperative care. The pediatric ERAS® component society was formed within the auspices of the ERAS® Society (www.erassociety.org). A board was elected among members of attendees, and a workgroup was established to establish position statements as medical evidence for pediatric ERAS became available.

Unique Pediatric Considerations

Historically, it often takes several years for major advancements in adult surgical care to be adopted into pediatric care. However, it is likely that many of the same benefits conferred by ERAS to adult patients can also be obtained in children. A major challenge that makes pediatric ERAS particularly unique is the wide range of ages and development stages of children who present for surgical procedures. Indeed, a pediatric surgeon can perform operations on very-low-birth-weight premature infants with congenital heart disease and healthy teenager athletes on the same day. Though populations of children in all stages of development may benefit from pediatric ERAS pathways (Fig. 58.1), the individual components will vary greatly given the vast differences in physiology, energy requirements, pharmacodynamics, and psychological maturity. Similar to adult ERAS pathways, a highly effective multidisciplinary pediatric ERAS team consists of well-aligned surgeons, anesthesiologists, pain management physicians, intensive care unit (ICU) physicians, nurses, and advanced practice providers all working in synergy to make the pathway successful and sustainable. Other healthcare providers such as pediatricians, neonatologists, pediatric intensivists, pediatric physical therapists, lactation consultants, child psychologists, child life therapists, and music therapists are unique members of pediatric perioperative teams who may provide useful services in pediatric ERAS pathways. A major aspect of ERAS pathways is preoperative education, setting expectations, and empowering patients to become active participants in their own postsurgical recovery pathway instead of passive recipients of care. Analogously, empowering parents and/or caretakers to participate in their child's recovery process can help promote a sense of structure to the child who is likely experiencing confusion, stress, and anxiety in the perioperative period.

Outcome measures that are common to many adult ERAS pathways may also be extrapolated to pediatric ERAS, but unique pediatric factors must also be considered. Adult and pediatric ERAS pathways typically focus on reduced complications, LOS, opioid use, perioperative nausea, surgical site infections, and readmission rates. These metrics are just as important in pediatric perioperative care as they are in adult perioperative care. Certain metrics that are relatively straightforward to understand in adult surgical populations are much more challenging to quantify in children due to the

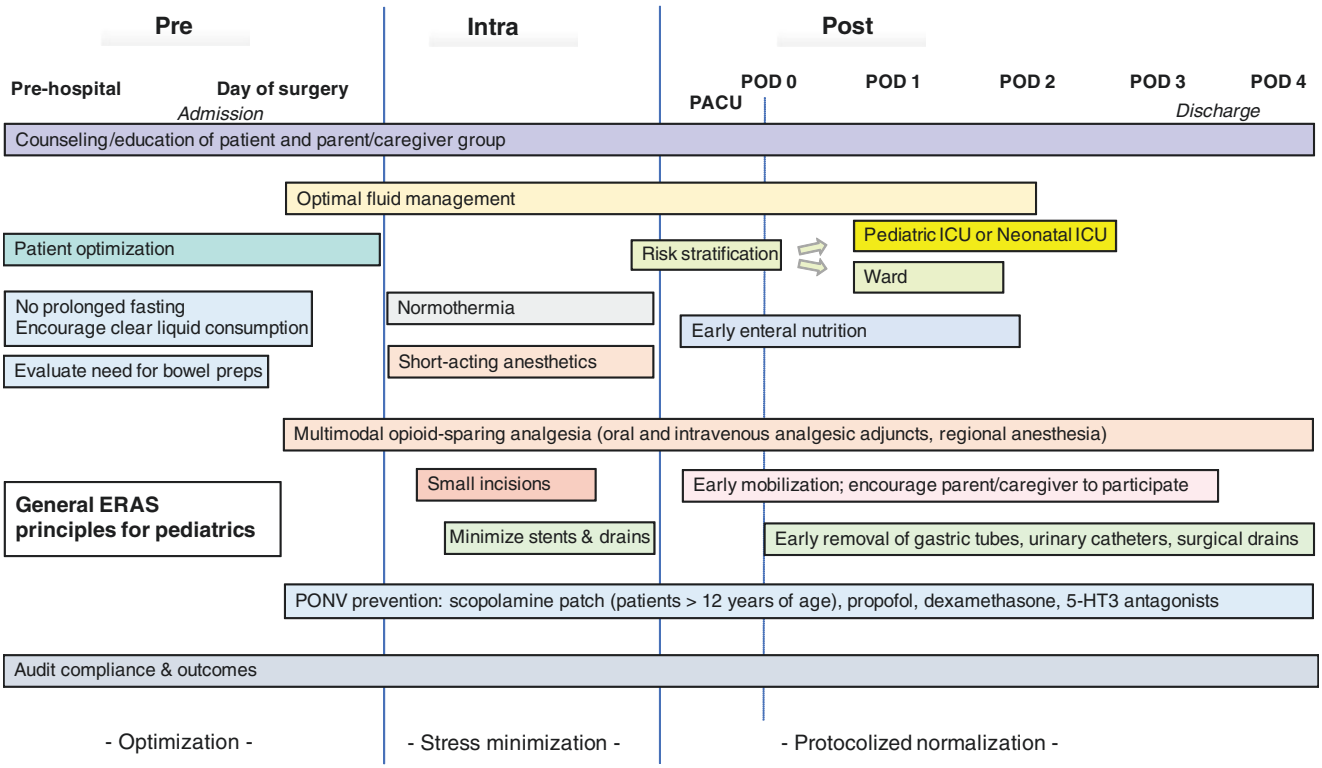

Fig. 58.1 General ERAS principles for pediatric surgery. PACU postanesthesia care unit, ICU intensive care unit

great variability in patient age and developmental stage as noted above. These unique metrics include preoperative bowel preparation, surgical nutrition, perioperative fluid management, opioid-sparing analgesia, and patient/family satisfaction scores. Additionally, better metrics, designed to assess the psychological impact of the stress of surgery on the child and their caregivers, may be needed to fully assess the patient and family experience.

Perioperative Analgesia

Optimizing perioperative analgesia is an important facet to most ERAS pathways. As in adults, the basic goal of perioperative analgesia in children is to allow for rapid return to baseline functional status. Secondary goals include reducing overall opioid analgesic consumption and the risk of progression to chronic postsurgical pain. Opioids are effective analgesics but are fraught with a myriad of side effects. Opioid-induced respiratory depression, pruritis, nausea, bowel dysmotility, and somnolence all have the potential to prolong or complicate surgical recovery. Many of the adverse effects of opioids are more pronounced in children, particularly neonates and children with significant coexisting disease. The worldwide opioid epidemic, particularly severe in the United States, is most widely reported and studied in adult populations, but children have certainly not been spared. Children become collateral victims of the opioid crisis in a number of ways including neonatal exposure, accidental ingestion by young children, and intentional ingestion by teenagers accessing unused medically prescribed opioids. In fact, opioid overprescribing after surgery is one of the most important risk factors in the development of opioid misuse in older children [7]. In the pediatric urologic population, children are prescribed nearly 10 excess doses of opioids, corresponding to 62% of leftover unused opioid after surgery [8]. These excess opioids lead to excessive pill burden in communities, which can lead to diversion and/or misuse of these analgesics. Teenagers who possess opioids for a period greater than 2 weeks have a 50% higher risk of opioid-related side effects (often misuse) compared to teenagers who possess opioids for less than 5 days [9]. Intraoperative and postoperative use of adjuvant analgesics such as anticonvulsants (gabapentin, pregabalin), ketamine, dexmedetomidine, clonidine, acetaminophen, intravenous lidocaine, and nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce the overall perioperative requirement for opioids in children as in adults. Pediatric chronic pain is a poorly recognized clinical entity. However, postsurgical pain that persists for 3 months or longer after a pediatric surgical procedure is reported in 10–50% of children, depending on the surgical procedure. The greatest risk factor for progression to chronic pediatric postsurgical pain is poorly managed acute pediatric postsurgical pain. Pediatric ERAS protocols that include robust multimodal opioid-sparing strategies are able to reduce all of these risks while contributing to rapid return of physical functioning.

Regional anesthesia is a common facet of many adult ERAS pathways and may be applicable to pediatric ERAS as well. Reduced opioid requirement, fewer opioid-related adverse events, and less sedation may all be conferred by regional anesthesia techniques. The safety of peripheral nerve blocks, neuraxial blocks, and truncal blocks in children has been well established by several studies originating from the Pediatric Regional Anesthesia Network (PRAN). The PRAN is a collective registry of pediatric regional anesthetic techniques submitted by more than 20 member children's hospitals. The most recent analysis of more than 100,000 pediatric regional anesthetic techniques showed a very low risk of complications with no reports of permanent neurologic deficits [10]. Other studies have confirmed the safety of performing regional anesthesia procedures under general anesthesia—a common requirement for young children unable to tolerate such procedures awake [11]. Regional anesthesia techniques incorporated into pediatric ERAS protocols should be seen as a component of a comprehensive multimodal analgesic regimen instead of a sole analgesic technique. Indeed, much of the literature surrounding the use of regional anesthesia also utilizes other multimodal non-opioid analgesic agents including gabapentin, acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and ketamine [12]. Epidural catheters and paravertebral catheters have been shown to be effective in enhanced recovery for pectus excavatum surgery in children when paired with other intravenous (IV) and/or oral opioid-sparing adjuncts [13]. Truncal blocks such as transverse abdominis plane (TAP) blocks and rectus sheath blocks are important components of pediatric ERAS protocols for major urologic reconstructions and other pediatric intra-abdominal surgical procedures [14]. Continuous truncal catheters have also been placed for regional blockade after these surgical procedures. The role of peripheral nerve blocks or continuous peripheral nerve catheters has not been reported as components of pediatric ERAS protocols. However, a robust pediatric pain service that supports a peripheral nerve catheter program may allow for transition of a surgical procedure that typically requires overnight inpatient admission for pain control to an ambulatory procedure [15, 16]. Though regional anesthesia may confer the aforementioned benefits, practitioners must be aware that these procedures introduce unique risks and additional costs to perioperative care. Like other ERAS components, the true benefit of adding regional anesthesia to ERAS protocols must be weighed against these risks/costs.

Pediatric General Surgery ERAS

Several studies have evaluated the efficacy of various iterations of ERAS pathways for children undergoing pediatric surgery. One retrospective and four prospective cohort

studies, evaluating children undergoing gastrointestinal (GI), urologic, and thoracic surgeries, were identified for a systematic review conducted in 2016 [17]. Each study included ≤6 elements compared to the 20 or more elements recommended by most adult enhanced recovery protocols. Despite inconsistent outcomes and no adequate controls, the studies suggest appropriately applied ERAS protocols in pediatric surgery may decrease LOS and opioid use, with no additional complications. A national survey of pediatric surgeons' opinions, regarding the applicability of the 21 widely accepted ERAS elements to pediatric surgery, was conducted through the American Pediatric Surgical Association (APSA) [18]. Of ~1052 members, 257 completed the survey (24%). Most respondents (n = 175, 68%) reported being "moderately," "very," or "extremely" familiar with ERAS protocols. However, only 19% (n = 49) reported "already implementing" an ERAS protocol in their practice. Most respondents (67%) reported "already doing" or "definitely willing" to implement 14 of the 21 ERAS elements. Ten percent of respondents reported being only "somewhat willing," "uncertain," or "unwilling" to implement the seven remaining elements: avoidance of mechanical bowel preparation, avoidance of prolonged perioperative fasting, use of venous thromboembolism (VTE) prophylaxis, use of a standardized anesthetic protocol, avoidance of routine nasogastric tube (NGT) use, use of goal-directed fluid therapy (GDFT), and use of insulin to control hyperglycemia [18].

Based on the national survey results, a multidisciplinary, expert panel was assembled, representing 11 children's hospitals from across the United States and including 8 pediatric surgeons, 3 pediatric anesthesiologists, 2 pediatric gastroenterologists, 2 patient representatives, and 1 nurse practitioner. A modified Delphi process, using the Rand/UCLA method, was conducted to review the literature, discuss, and reach consensus on the inclusion of the seven controversial ERAS protocol elements [19]. Five of seven elements were selected for inclusion in the modified pediatric ERAS protocol for GI surgery. The two excluded elements were (1) avoidance of mechanical bowel preparation prior to surgery and (2) the use of insulin to maintain normoglycemia in the perioperative period. The final elements of the pediatric surgical ERAS protocol for gastrointestinal surgery are shown in Table 58.1.

To assess feasibility of implementing the ERAS protocols in pediatric gastrointestinal surgery, as well as its preliminary effectiveness, a pilot study was conducted using a multidisciplinary implementation team at a single pediatric surgical center [20]. Data were collected from the electronic health records of 43 patients in the pre-ERAS period (2012–2014) and for 36 patients in the post-ERAS period (2015–2016). Outcomes of interest included number of ERAS elements received, median LOS, complications, and 30-day readmission. Most pre-ERAS (91%, n = 39) and post-ERAS (80%, n = 31) patients had a diagnosis of inflammatory bowel disease, with most surgeries being ileocecal resections and colectomies. Key ERAS approaches to pain management included using non-opioid analgesics preoperatively, employing neuraxial blocks, and coaching patients with mental imagery, mindfulness, and breathing exercises. There was a steady increase in the number of ERAS elements being used, over time, with a simultaneous decrease in LOS from 5 to 3 days (p = 0.01). In the post-ERAS cohort, decreases in median time to regular diet (2 days to 1 day, $p < 0.001$), median dose of intraoperative opioids (0.452 morphine equivalents mg/kg to 0.07 morphine equivalents mg/kg, $p < 0.001$), median dose of postoperative opioids (0.73 to 0.07 mg/kg, $p = 0.001$), and median volume of intraoperative fluids (9 to 5.4 mL/kg/h, $p \leq 0.001$) were noted. There was a trend toward reduced complication rates (21% vs. 17%) and 30-day readmission rates (23% vs. 11%) in the post-ERAS cohort, although statistical significance was not reached. Follow-up studies of this same population demonstrated decreased opioid prescribing at discharge for these patients as well as sustained improvements in the previously reported outcomes [21].

These preliminary results suggest that implementation of a pediatric-specific ERAS pathway for pediatric abdominal surgery is effective, safe, and leads to shorter LOS, reduced opioid use, and improved outcomes. Implementation was found to be feasible, with strong buy-in, engagement, and widespread endorsement of the ERAS pathway by pediatric surgeons, gastroenterologists, anesthesiologists, pain management experts, nurses, and families. Future efforts under development include a prospective, multicenter implementation and effectiveness of ERAS pathways in GI surgery for children with inflammatory bowel disease.

Table 58.1 Pediatric surgical enhanced recovery elements for gastrointestinal surgery

Preoperative	Intraoperative	Postoperative
Patient/family education/engagement	Venous thromboembolism prophylaxis	Avoiding intraperitoneal/perianastomotic drains
Provider education	Pre-incision antibiotic prophylaxis	Goal-directed/near-zero fluid therapy
Optimize medical comorbidities	Standardized anesthetic protocols	Avoiding or early removal of urinary drains
Avoid prolonged fasting	Minimally invasive surgical techniques	Prevention of ileus through gut stimulation
Administer non-opioid analgesia	Prevention of nausea/vomiting	Opioid-sparing pain regimens
	Avoiding nasogastric tubes	Early oral nutrition
	Standardized hypothermia prevention	Early mobilization
		Audit protocol compliance/outcomes

Pediatric Urology ERAS

The first pediatric ERAS studies by Reismann included several urologic operations, including hypospadias repair, pyeloplasty, and nephrectomy [2, 3]. While these early studies suggested significant improvements in LOS without an increase in complications or readmissions, the authors note that during the periods studied, minimum LOS requirements were mandated for full reimbursement in Germany not necessarily reflective of wider practices. These criticisms notwithstanding, the authors demonstrated value in standardization of perioperative care within urology, setting the stage for improved implementations and studies within pediatric urology [22].

In 2014, a pediatric ERAS protocol was implemented at a tertiary care, free-standing pediatric hospital for patients undergoing urologic reconstruction as a prospective pilot study [14]. The protocol included 16 total items adapted from adult ERAS urology protocols, including elements like preoperative carbohydrate drink, avoidance of bowel preparation, euvolemia, minimization of opioids intra- and postoperatively, and early diet (clears night of surgery, regular diet next day). Patients between the ages of 4–18 years undergoing operations that included a bowel anastomosis (bladder augmentation and/or creation of a continent catheterizable channel such as an ileovesicostomy) were included. No exclusion criteria were defined. Thirteen patients were enrolled, and propensity matched to 26 recent non-ERAS historical controls (2009–2014) with no differences seen in baseline variables.

Length of stay fell from median 6 days historically (interquartile range [IQR] 5–7) to 5 days in the ERAS cohort (IQR 3–6). National mean LOS for these procedures ranges from 7 to 10 days [23, 24]. The small pilot nature of the study was underpowered to show significant differences in LOS. ERAS process measures increased significantly from median 8/16 protocol items historically (IQR 4–9) to 12/16 (IQR 11–12) under ERAS. The largest differences were seen in early discontinuation of intravenous fluids, achieving opioid-free intra- and postoperative analgesia, and early feeding, highlighting the importance of these items. Balancing measures of emergency department visits, readmissions, and reoperations did not increase with ERAS. Importantly, the authors found a significant decrease in 90-day complications that went from 2.1 per patient historically to 1.3 per patient under the ERAS protocol ($p = 0.035$), demonstrating the potential for standardization of pediatric perioperative care to minimize variation from patient to patient and improve outcomes.

One area that continues to pose some difficulty in studying pediatric ERAS for urology and all other pediatric surgical specialties is the lack of definitions for opioid minimization—an important pillar in the ERAS protocol. As part of the pilot study above, the threshold to meet the intra- and postoperative ERAS process measures was set at zero, not out of seeing this as a reasonable outcome but with the goal that the multidisciplinary implementation and multimodal pain control would limit opioids and allow collection of pilot data reflecting opioid minimization. In all, only two patients (15%) were found to be opioid-free during both the intra- and postoperative phases of care. The authors determined that thresholds of 0.30 mg/kg IV morphine equivalents intraoperatively and 0.15 mg/kg/day IV morphine equivalents postoperatively covered 75% of patients in the study. These limits have been incorporated into newer protocols accompanied by explicit statements that pain should be treated, and patients are written for standard doses and frequency of opioid pain medication as a third-line intervention.

Neonatal ERAS

Neonatal ERAS represents a significant departure from adult and most pediatric ERAS guidelines. While older adolescent surgical patients may often be effectively treated with modified adult ERAS guidelines, neonatal surgical patients require a radically different approach. Neonatal surgery presents the extreme end of physiologic challenges. Neonatal ERAS guidelines need to address the unique physiologic needs of newborns including nutritional requirements (with competing energy requirements for growth and healing), exquisite sensitivity to fluid over- and under-resuscitation, temperature instability, and a markedly different immune response to surgical stress. Surgical site infections (SSIs) in neonates have been reported to be 13.5% in population-based studies, which is more than twice that commonly reported in adults [25]. SSIs in these infants are associated with poor growth, longer hospital stays, need for reoperation, and mortality. The social and communication issues of neonatal surgery are also unique, with an important role played by the neonatology team and key involvement by parents throughout an infant's surgical journey.

Despite these dramatic differences, neonates are particularly well-suited to the ERAS approach, and evolving guidelines will likely offer tremendous opportunities to improve care. Neonatal surgery is characterized by high degrees of variability with many areas where best practice remains unclear and decisions are influenced by teams of changing neonatologists, surgeons, anesthesiologists, and nursing staff in addition to parents [26]. Optimizing the use of evidence-based care and minimizing variability can and has improved outcomes for this population [27, 28].

The development of the first neonatal surgical ERAS protocols is ongoing, and recommendations will address some of the important themes of ERAS while concentrating on the unique needs of these patients [29]. Some examples of these recommendations include those related to nutrition: the importance of early, oral feeding with breast milk, which can

improve intestinal immunity, shorten time to feed, and time in hospital [30, 31]. Additionally, recommendations for multimodal pain management reflect unique methods of neonatal analgesia: the use of caudal anesthetics (effective pain relief in appropriate cases with low complication rates) and the use of oral sucrose (diminish pain during minor procedures) [32, 33]. The involvement of parents within neonatal ERAS will be a key to its success. The process of hospital discharge for neonatal surgical patients has been characterized by parents as rushed and confusing with inconsistent communication [34, 35]. Allowing parents to participate in the care of their child and providing opportunities for education throughout the hospitalization increases parental knowledge, confidence, and satisfaction. In addition, this approach has also been associated with improved infant developmental outcomes, increased compliance with well-baby checks, and reduced emergency room visits [36–38].

Neonatal surgical care is well-suited to ERAS, although the unique needs of these patients require novel approaches. As neonatal ERAS guidelines develop, ongoing re-evaluation will be required to optimize the effectiveness of these tools.

Pediatric Orthopedic ERAS

While the official ERAS label has not been adopted to a significant degree in the perioperative management of pediatric patients undergoing orthopedic surgery, "ERAS-like" or enhanced recovery protocols have been developed for some surgical procedures. Pediatric orthopedic surgery falls into three major categories based on presentation: emergent, urgent, and elective. Emergent orthopedic surgery is common in children given the relatively high rate of musculoskeletal trauma in pediatric populations. However, early efforts to develop and implement ERAS principles have taken place in elective surgery such as the adolescent idiopathic scoliosis (AIS) population undergoing elective posterior spine fusion.

AIS is the most common skeletal deformity in children with approximately 5000 posterior spine fusions performed annually in the United States [39]. Historically, length of stay for this surgery was 5–7 days. However, in recent years, a number of institutions have reported on the implementation postoperative protocols designed to improve the quality of recovery by reducing dietary restrictions, advocating for early ambulation, and implementing multimodal analgesic strategies with less focus on preoperative or intraoperative management. One retrospective review compared outcomes in consecutive patients managed with a "standard pathway" or an "accelerated pathway," which included a preoperative education session to prepare patients for the recovery process [40]. Postoperatively, the accelerated pathway included early transition to a solid diet on postoperative day (POD) 1, early removal of the urinary catheter (POD 1) and surgical drains (POD 1–2) with physical therapy (PT) mobilization on POD 1, and early transition to oral opioids on POD 1 with removal of the patient-controlled analgesia (PCA) pump and initiation of ketorolac on POD 1. These interventions reduced LOS from 4.2 to 2.2 days on average without increased complications. Other investigators, using a quality improvement approach, reported on the development of a "rapid recovery pathway," which included similar practice changes postoperatively as well as preoperative use of gabapentin and acetaminophen, intraoperative methadone, and a multimodal analgesic strategy postoperatively [41]. This group also reported a reduction in LOS from 5.7 to 4 days and reported that pain scores were not worse and possibly better on POD 0 and 1 despite early PT work. Finally, two investigators have reported on the adoption of the American Society of Anesthesiology (ASA) model of the Perioperative Surgical Home (PSH) in the management of posterior spine fusion [42, 43]. Unlike the pathway work described earlier, which focused primarily on the postoperative care, PSH models of care are designed to standardize the three epochs of care: preoperative, intraoperative, and postoperative with the goals of streamlining care and reducing variation and cost. As such, the PSH model closely mirrors the ERAS model of care, but the PSH care models are typically institutional specific and are not meant to generate evidence-based guidelines though evidenced-based practice is certainly a foundation of the PSH. Thomson and colleagues reported on a PSH model of adolescent posterior spinal fusion that resulted in reduced rates of crystalloid administration, reduced perioperative transfusion, and reduced LOS [43].

Moving forward, more work needs to be done to develop and integrate evidence-based guidelines into an ERAS model for pediatric spine care that includes recommendations regarding preoperative care and preparation, intraoperative management including fluid and blood management, and postoperative care [44, 45]. Once established, the pediatric spinal fusion ERAS guidelines can serve as a model for the development of other pediatric-specific orthopedic guidelines, including the management of neuromuscular patients undergoing spine fusion or complex lower extremity reconstruction, patients presenting for complex hip reconstruction or preservation surgeries including periacetabular osteotomy, and pediatric patients presenting for complex knee surgery including anterior cruciate ligament reconstruction. There is much enthusiasm for the type of coordinated care that ERAS fosters, and, fortunately, much of the groundwork for comprehensive procedure-specific guidelines is already in place.

Conclusion

Pediatric ERAS is currently in the early stages of development but has clearly shown benefit in general surgery and urology populations, with promising advances being made in neonatal and orthopedic surgery specialties. Reductions in

perioperative complications, opioid consumption, and length of stay are important metrics by which the effectiveness of pediatric ERAS pathways may be measured. However, considerable work needs to be done to understand the role of components such as bowel preparation, perioperative nutrition, analgesia, and fluid management. ERAS in pediatric surgery has tremendous potential to not only improve quantifiable perioperative metrics but to significantly improve the surgical experience of children across the world.

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Part IX

Administrative

Department-Wide Implementation of an Enhanced Recovery Pathway: Barriers and Facilitators

59

Deborah J. Watson and Claudiane Poisson

Introduction

Enhanced recovery after surgery (ERAS) uses a multimodal approach facilitating patients to recover faster from surgery. ERAS challenges traditional care and brings a paradigm shift toward a modern, evidence-based surgical care delivery. After initial success in colorectal surgery, the ERAS concept has demonstrated benefits in many other specialties including thoracic [1, 2], urologic [3], gynecologic [4], pancreatic [5], oral and maxillofacial [6], orthopedic [7], hepatobiliary [8], and bariatric surgeries [9]. A care pathway is a valuable tool to help guide both staff and patients as what to expect during the hospitalization period and beyond. These care pathways also help decrease variability, errors, and length of hospital stay [10–12]. Vanhaecht [13] defined the term "care pathway" as a complex intervention for the mutual decision-making and organization of care processes for a well-defined group of patients during a well-defined period. Patients who adhere to an enhanced recovery pathway (ERP) are less likely to develop postoperative complications and be readmitted to hospital. They are also more likely to have a shorter hospital stay and a faster recovery. The implementation of a colorectal ERP has been shown not only to be cost-effective for the institution but also for the healthcare system and for society in general [14]. Still, the change in practice remains slow and can take up to 17 years to bring evidence to the bedside [15]. Moving away from conventional practice can be challenging and requires us to encompass a multitude of elements to integrate within the preoperative, intraoperative, and postoperative phases. Developing an ERAS culture in a hospital or within a department takes more than written protocols or guidelines. It takes patience, leadership, passion, vision, determination, and at times resilience.

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Barriers to implementation of an ERP are perceived differently by healthcare providers [16]. A lack of support from the organization, limited resources, poor leadership skills, and resistance to change may hinder its implementation [16–18]. In contrast, there are several enabling factors that support implementation such as having a committed leadership team that meets on a regular basis, support from the hospital administration, and local champions committed to initiate this change [19]. Scholars have described their experiences in implementing ERP, offering solutions to decrease barriers while also highlighting facilitators [16, 20]. Nonetheless, there is no "one size fits all" approach, and selecting and tailoring implementation strategies linked with barriers of your own institution are important. Despite having valuable management strategies and key enablers to bring change successfully inside an organization, the ideal implementation of an ERP has not been defined clearly and requires further study [18, 21].

This chapter identifies best practices that should be considered while initiating an ERP and provides insights for implementing at a departmental-wide level. It covers a step-by-step plan from the creation, implementation, evaluation, and, finally, to the sustainability phase. It elaborates on key approaches to change management, names strategies to help bring change positively in healthcare practices, and identifies some common barriers that could hinder the implementation process of an ERP within a department. It also recognizes significant components that are at the foundation for a successful start of an ERAS program. Finally, it highlights the importance of evaluation so that efforts and resources are not wasted and that the processes do not revert to their former status.

Creating an Enhanced Recovery Pathway

Obtaining Department Buy-In

Acquiring the staff's buy-in will facilitate this change initiative. A few components must be considered when introducing an ERP within a surgical and anesthesiology department.

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A top-down or a bottom-up management style can both be effective. Whereas each has advantages and disadvantages, the latter is observed more often in the hospital setting in the form of lead physicians who wish to start ERAS practices for their patients [22]. Nevertheless, the implementation of an ERP will be facilitated if the administration supports the change [18]. The upper management and middle management need to encourage and approve this quality initiative so that at the very minimum the multidisciplinary team has the allotted time for regular scheduled meetings to discuss the care pathway and plan accordingly. An organization that is not open to change and that does not support this initiative may interrupt and end the program [18].

Behaviors such as the ability to motivate, communicate, and build a team have been linked to predictors of successful organizational change [23]. There is less likelihood for a change initiative to face resistance if the change is communicated in a well-timed matter [24]. Good communication between the leadership team and clinicians facilitates the implementation of a new practice change [18]. Frontline nurses are the healthcare professionals that spend the most time with hospitalized patients, and therefore they should be involved in the development and implementation process from the beginning. Introducing the evidence-based concepts of ERAS, identifying the team members working and supporting this change initiative, explaining the potential modifications to everyday tasks and responsibilities, clarifying the reasons for this departmental change, and the timeframe for the launch date are all topics that should be shared with the frontline staff from the very beginning. Articulating the vision, giving information, listening to frontline staff, and providing plenty of opportunities for staff to voice concerns should also be prioritized. People who resist change might enumerate barriers, and this will be beneficial since these obstacles should be identified and addressed prior to implementation. Starting a departmental ERP will not be a linear progression process from beginning to end; adjustments and revisions are to be expected until the processes are fine-tuned and while issues are resolved locally. Gathering keen and eager staff to form a working group is part of the preliminary phase.

Creating a Leadership Team

Assembling a cohesive multidisciplinary team to lead the ERP should be the first step prior to the implementation [18, 19, 25]. The notion of teamwork and increasing communication is fundamental for eliminating fragmented care and breaking down the silos within the disciplines of each perioperative phases. Discussions between the preoperative, intraoperative, and postoperative healthcare providers are essential so that all disciplines are aware of how their own interventions impact the next phase, including the overall patient outcomes. Engaging local opinion leaders—in particular those who are perceived as trustworthy and influential within the department—may also enable this change [26]. Each team member needs to advocate for this initiative and act as change champion.

At the beginning, members of this core team should meet regularly in order to set the momentum, create a sense of urgency, and demonstrate that the status quo is no longer acceptable [19, 27]. At a minimum, three health disciplines should form the leadership team: a nurse, an anesthesiologist, and a surgeon [19]. Including a senior manager in the team may also help to attain institutional management support [21]. In our hospital, a surgeon, an anesthesiologist, a senior nurse manager, an ERAS nurse coordinator, a physiotherapist, and a nutritionist were at the core of the initial working group. At the beginning, we had a clinical epidemiologist involved in the team to help with evidence review. Now we have the benefit of a librarian to first filter through the abundance of the literature on existing guidelines and, second, to look for the best evidence if we are struggling to reach consensus on a specific treatment or medication. Other allied health professionals such as pharmacists, social workers, occupational therapists, and stoma therapy nurses may join the leadership group when relevant. Naming a champion, from each healthcare discipline, should facilitate the change process [26].

Mapping all care processes and identifying all the people involved in perioperative patient care should help determine who should receive explanations about the changes prior to the launch date so that the patient receives consistent information from all hospital workers. In our institutional experience, we have a core steering committee team responsible for implementing pathways across the entire surgical department. This core team then works with individual surgeons, anesthesiology, and nursing experts for each new pathway. This allows us to extrapolate experience to facilitate creation of each additional pathway, regardless of specialty or procedure, as there may be overlapping processes. The clinical experts are then able to communicate the changes to their groups, giving a sense of ownership to the pathway and also providing occasions for research and academic opportunities for each surgical division.

Assigning a Care Pathway Coordinator

Appointing a full-time dedicated nurse or healthcare professional to the creation, implementation, evaluation, and sustainability of the ERAS pathway should be considered—especially if the team is creating multiple pathways across multiple disciplines at the departmental level [19, 21, 25]. The coordinator will provide consistency and experience to expedite development and implementation. Excellent communication skills, resourcefulness, and creativeness are key attributes of the coordinator to get everyone on board with this organizational change. The coordinator is also tasked with project

management, including scheduling and organizing meetings, writing drafts of the ERAS pathway, communicating between the core team and frontline staff, and assuring that all stakeholders have approved the final order sets [25]. Providing continuing educational sessions to staff, creating patient educational material, applying change management strategies, sending reminders, auditing and reporting the results to the unit may also be added to the tasks [18, 25]. Ljungqvist et al. [19] specified that the coordinator plays a fundamental role and "is the engine of the ERAS team."

Seeking Patient and Family Involvement

Patient engagement and participation are increasingly recognized as vital components of healthcare quality-improvement initiatives. We ask patients to provide specific insights at important points of the development process. This includes the pre-implementation meeting to review the final drafts of the order set and a post-implementation meeting to share their experiences while they were hospitalized. Obtaining positive and negative information regarding a patient's surgical journey when following ERAS can be a very enriching experience for both the patients and the leadership team. Patients may feel empowered to share their experiences. Meanwhile, the leadership team may feel encouraged to hear the positive experiences from patients, but, on the other hand, aim to continue improving the actual processes where needed. Patients and families may have different beliefs and expectations about what is considered excellent healthcare. For example, the benefits of a short hospital stay may not always be well perceived by patients [28]. Diverse cultures and previous experiences may influence acceptance of a change process [26]. Increasing patient engagement and seeking a patient and family partnership so that a more active role is taken toward recovery are worthwhile goals.

Developing Content

Gathering baseline data regarding the most prevalent surgeries, the length of hospital stay, complications, and readmissions will help the leadership team identify surgical procedures that may particularly benefit from implementation of ERAS. Subsequently, the team must decide whether existing literature should be used to build the care pathway from scratch or whether a pre-existing pathway could be adapted to their local environment. The ERAS® Society and other organizations—the American Society of Colon and Rectal Surgeons (ASCRS) and the Society of American Gastrointestinal Endoscopic Surgeons (SAGES)—offer guidelines for various surgeries [29] that can direct the team on the content to be prescribed and may be adapted to one's institution. Bringing change in an organization will be facilitated and face less resistance if the change is supported by evidence [26].

The ERAS® Society cites 24 perioperative elements that implemented together have a synergic effect that impacts surgical outcomes [19]. While some are specific to a surgical procedure, many similarities exist between various procedures, and having a single steering committee and coordinator facilitates operationalizing these pathway elements. Integrating these elements within the care pathway is an important action toward introducing the changes in practice. Different institutions may approach each element differently, depending on their resources and experience. Reviewing examples of different order sets from different institutions may help teams design their own pathways [30].

Writing a draft of the content and integrating it into the hospital's templates and electronic medical record program facilitate usage of the order set. We avoid creating order sets that include a list of optional checkboxes as we aim to decrease variability. Providing additional space to add specific orders if needed allows for flexibility.

Once all stakeholders have approved the content, writing the patient educational material may be started so that it can be launched simultaneously with ERAS. The first ERAS element included in the preoperative phase is pre-admission counseling. If we want patients to participate in their care, we must first ensure that patients and their families understand how they can play a more active role in their recovery. The preoperative information, started at the surgeon's office and reinforced by preoperative nurses, needs to explain the surgery and address how to prepare for surgery and what to expect after the surgery. Verbal explanation should be reinforced with written content by referring patients to either comprehensive websites or/and providing patients with printed material. The patient education material represents the care pathway written in a format understandable to patients. The content should be written in plain language, avoiding the usage of acronyms or medical jargon. Using *health literacy universal precaution* practices by simplifying information will ensure that all patients, regardless of their literacy levels, will understand the conveyed messages [31]. Adding meaningful images may help patients better understand the content [32]. Leaving plenty of white space and writing short sentences in point form may also encourage patients to read the instructions [33, 34]. Once all the content, including the order set and the patient education material, is finalized, determining an implementation action plan including identification of barriers is the next step.

Identifying Potential Barriers

ERAS and all the changes they bring in daily practice can meet different barriers, especially at the beginning of the implementation [35]. Barriers to a change initiative are multifactorial and are regrouped under three distinct categories:

(1) patients and their families, (2) clinicians, and (3) healthcare organizations [26].

Patient characteristics can be a barrier to implementation, such as low socioeconomic status, comorbidities, age, and non-compliancy with their treatment [17, 18]. In their qualitative study, Lyon et al. [28] highlighted that patient expectation to care was a barrier to ERP implementation. When patients had unrealistic expectations with the postoperative care, it became difficult for them to comply with certain elements such as mobilization and nutrition. In addition, patients receiving inadequate perioperative information as to what to expect during and after surgery was also cited as a barrier [17]. These patients indicated unexpected difficulties at home after surgery that could have been resolved with adequate patient education. Caregivers need to communicate and reinforce the same information to patients consistently. More importantly, staff should familiarize themselves with various teaching methods to increase patient knowledge and understanding and use a plain language approach during patient education [33, 34]. For hospitalized patients, knowledge of their daily goals and schedule for the day is important [36]. Our patient education material describes milestones for each day for nutrition, mobilization, pain, and drains, as well as the target discharge date. White boards in each room are used to emphasize these goals to the team and increase communication between patients and their families and the healthcare team.

Attitude, behaviors, and knowledge from healthcare providers also may be a barrier to effective functioning of the ERAS program [17, 18, 20, 28]. Senior clinicians were found to be more resistant to ERP guidelines than junior staff [28]. Yet, younger clinicians were less familiar with the care pathway concepts and less likely to follow the postoperative guidelines [37, 38]. Pathways may be perceived as being too rigid, overly prescriptive, "cookbook medicine" leaving no room for critical thinking and threatening autonomy [10, 17]. Alawadi et al. [17] also mentioned that healthcare professionals were resistant to change because ERP modified their habits and work routine. Providing education to increase staff knowledge may reduce resistance to this change practice [18]. Siloed communication between the different stakeholders, clinicians, and staff can be a major difficulty and impact the process [17, 18, 20].

Rotating resident physicians may be a barrier if they are not informed of the departmental ERP when they start a new rotation [16, 17]. Resident physicians need to receive the necessary training to become familiar with the ERP and how to prescribe the various components to ensure that the process flows well. Engaging the residents is a worthwhile investment as they are the future surgeons and anesthesiologists that will carry the concept of ERAS over to the next generation. We provide an annual informative session to first- and second-year resident physicians that include the evidence-based principles of ERAS, the processes established in our hospital, the outcomes of our program, and the health literacy concept. Identifying an ERAS resident champion has also been mentioned to help engagement and promote the program among their peers [39].

Finally, organizational factors can be barriers to implementing an ERP. Lack of material and financial resources, recurrent staff turnover along with a deficit in human resources can impact the consistency of the practice and implementation [17, 19, 20, 28]. The lack of weekend staffing of stoma therapy nurses may also create a bottleneck for stoma patients needing support and teaching prior to going home. Stone et al. [18] defined the organizational culture as the values and norms that may impede a successful implementation of an ERAS program. Once all barriers have been recognized and decreased or eliminated, planning the rollout follows.

Implementing an Enhanced Recovery Pathway

Moving into Action

Successful implementation of ERAS can be challenging to achieve because of the many healthcare professionals involved in perioperative interventions [18]. Despite having strong evidence supporting each ERAS element, adherence in daily practice can be difficult [35]. Knowledge transfer frameworks and implementation programs can be used as references to guide this change initiative and to ease the implementation. After all stakeholders have approved the order set as well as the patient education booklet, there may be an institutional process to revise the documents to meet hospital standards. Following this approval, a launch date can be established. A summary of our current implementation process is provided in Table 59.1. Before moving into action with the implementation, several activities need to be coordinated. A detailed plan should describe actions to meet targeted objectives: when, with whom, and how ERAS will be communicated and which resources will be needed. In our institution, the moving-into-action plan provides a timeline with specific and accountable actions and describes how and to whom the ERAS program will be disseminated among the different perioperative departments. The upcoming implementation is communicated by the coordinator to a wide audience: nurses, surgeons, residents, anesthesiologists, clerical staff, and other healthcare professionals who will be affected by the care pathway.

Communicating and Training the Perioperative Teams

To increase the success of the new practice change in the department, the coordinator needs to select different implementation strategies. A few weeks prior to implementation, a

Table 59.1 Summary of steps and actions to be taken when implementing a department-wide enhanced recovery pathway (ERP)

Steps	Actions
Creating an ERP	Obtain department buy-in
	Assemble an ERP multidisciplinary team
	Assign an ERP coordinator
	Gather preliminary surgical data
	Search for best evidence
	Develop content with surgical team specialists
	Seek patient engagement
	Approval of content with ERP core team
	Identify potential barriers
	Approval of content within institutions' committees
Implementing an ERP	Plan a launch date for implementation
	Communicate launch date with key stakeholders
	Educate nurses, resident physicians, surgeons, anesthesiologists
	Identify team champion
	Remind stakeholders of launch date
	Launch ERP
Evaluating an ERP	Audit ERP elements compliance
	Collect data on surgical outcomes and evaluate patient education material
Sustaining an ERP	Organize a postlaunch meeting with surgical team specialists and ERP core team to present audit results
	Revise and modify content based on audit results and champions' feedback
	Provide ongoing ERP education with clinicians

reminder should be sent to all stakeholders announcing the launch date and including a step-by-step plan of the new process. Reminders can be in paper or electronic formats such as posters in patients' charts or on department communication boards or as computer reminder alerts [26]. Several publications report that the most frequent facilitator of ERAS implementation is ongoing education to clinicians [17–19, 21, 28, 35]. Prior to the launch date, seminars should be offered to nurses, resident physicians, surgeons, and anesthesiologists to explain the order set and to overview the patient education material. These teaching sessions can take place in different formats such as face-to-face or e-learning platforms. The goals of educational sessions are to increase clinicians' knowledge, influence their perceptions, and subsequently to improve patient outcomes [26]. They can take place during orientation of new clinicians, weekly department meetings, department in-services, or ERAS workshops.

Clear communication across perioperative departments is critical to ensure an effective implementation. Arroyo et al. [40] reported practice change in larger hospitals was more complex and slower than in smaller hospitals. Alawadi et al. [17] supported this finding by stating that implementing ERAS in a small hospital structure is a facilitator because clinicians know each other, and communication is easier. On the other hand, ERAS pathways have been successfully implemented across a wide variety of hospital types and sizes [41]. Institutions putting in place ERAS guidelines for the first time might find it advantageous to implement at a smaller scale as a pilot project before applying it at a larger scale as the hospital standard of care. Demonstrating efficient preliminary results may help increase buy-in from healthcare clinicians and administration [42]. We collected and presented data on the impact of the earliest care pathways on outcomes including hospital stay to the surgical mission leadership group, which resulted in their investment in the resources needed to sustain and expand the program. Today, we have implemented more than 20 ERAS protocols in all the divisions of the department.

Team champions need to play an active role in the implementation by being a resource for other staff in their environment [26]. They are seen as facilitators and should engage frontline clinicians by using different activities, such as recognizing the importance of change, finding solutions to problems, and providing support to staff [26]. Other allied health professionals such as clinical nurse educators, whose main role is to educate frontline nurses on evidence-based practice, can support the adoption of the new practice and influence nurses to endorse the use of the care pathway. Nursing staff play a key role on surgical wards and a successful ERAS implementation depends on their acceptance of the new care pathway as well as the collaboration with anesthesiologists and surgeons [43]. On the implementation day and the following weeks, the coordinator should visit the departments implicated with this practice change to ensure pathway compliance, to support users in the transition by answering their questions, and to coordinate between perioperative departments.

Evaluating an Enhanced Recovery Pathway

Evaluation of care processes and outcomes is a key component of ERAS. This should begin prior to development of ERAS in order to have a comparison. Monitoring the practice change by evaluating the adherence with care processes examines if clinicians and patients are carrying out what is written in the order set, rather than solely tracking outcomes that provide the consequences or the final results. In the knowledge-to-action framework, Graham et al. [44] underline the importance of monitoring how a new intervention is being used by the adopter group. If the new intervention is not adopted as expected, knowing the reasons is useful to improve and to revise the implementation process. Audits need to be performed to evaluate compliancy with the ERAS elements. Patients' surgical outcomes improved when there was better compliance with the ERAS elements [45, 46]. Findings indicate patients had less postoperative complications, lower risk of postoperative symptoms that delayed discharges, and a higher tendency to meet the targeted length of stay [45]. Readmission rate, length of hospitalization stay, mobilization after surgery, complications,

resuming of normal diet, continuous protocol compliance, readiness for discharge, and patient-reported outcomes are the minimum numbers of elements that should be audited during hospitalization [21]. Although enumerating all of the outcomes that should be reported is beyond the scope of this chapter, patient-reported outcomes after discharge should perhaps also be audited to understand better when patients recover and ascertain the long-term benefits of patients enrolled in an ERAS program [47].

Contrary to common beliefs, Hubner et al. [43] found that nursing workload decreased when implementing a colorectal ERAS program. Their results showed that when there was an increased compliance to ERAS protocol, a decrease in nursing workload was observed. They suggested investing in a rigorous patient preparation regarding mobilization and nutrition as these impact the nursing workload. Eliciting feedback from patients' hospitalization experience could highlight factors impacting the process [17]. Patients can provide feedback about the preoperative education received. In our institution, following a care pathway launch, patient education materials are evaluated using a questionnaire so that we can monitor the patients' compliance on their usage and understanding of the content. Depending on the patients' feedbacks, the educational material is modified to incorporate their needs.

Besides auditing, other evaluation strategies can be planned. Feedback can be collected from clinicians through focus groups, post-implementation interviews, or questionnaires to understand clinicians' perceptions, team dynamics, and other issues occurring since the implementation [26, 48]. When questioned, most clinicians favored audits since it increased awareness of the improvements and then provided an opportunity to express themselves on the new interventions and to indicate any changes that might be required [49]. For example, our audit found a very low adherence with protein drinks. An organizational barrier surfaced upon interviewing the frontline nurses. They explained that when patients were transferred late to the ward, the diet orders did not get carried until the next day. We solved this issue by keeping protein drinks in the ward's refrigerator.

Collecting data from patients' charts is resource intensive and can also be challenging because of the lack of documentation, missing information, and even incomprehensive handwriting. Moreover, the integration of software may prove demanding as data may come from various sources and the capabilities to combine data together are inadequate. Few organizations have the capabilities of integrating different software to give one clear report [50]. Despite a relative high compliance in the early phase of the implementation, the compliance can decline rapidly without providing regular results on the effectiveness of the ERAS program [19, 35]. Auditing on a regular basis to evaluate if the outcomes are met, to assess if there is any discrepancy between the written protocols and the practice, and setting new goals for improvement will give the opportunity to upgrade the care pathway [49]. We have had a variety of data management and reporting solutions throughout the 10 years of our ERAS program. A simple Excel spreadsheet was first used to collect if the targeted discharged dates were attained and the reasons for not meeting these dates. To obtain a more comprehensive view, we used the ERAS(R) Interactive Audit System for several years, but in our high-volume center, this required a full-time auditor. The National Surgical Quality Improvement Program has a variety of enhanced recovery care process and outcome variables that can be used in participating centers [41].

Sustaining an Established Enhanced Recovery Pathway

The last phase closely related to the evaluation is the sustainability. Putting in place a constant review and feedback mechanism will help to sustain the ERAS program [19]. Major new projects often fail in the long run without ever achieving any significant results because no sustainability actions were initiated [51]. Parsons et al. [52] cited that "the sustainability is achieved when a process or outcome, at a minimum of a year later, has not returned to its former status…." Several factors facilitate the sustainability of a project, such as having strong organizational leadership who plans strategies to continue the change process [52]. Having a champion such as the ERAS coordinator will indicate that the change remains a critical priority for the organization and leadership team. In general, the role of ERAS champions is seen more informally, they are known locally in their departments, and they address practice gaps with the users [53]. Champions reported a sense of satisfaction when clinicians followed the colorectal ERAS protocol, and the elements were embedded in the practice [53].

Providing data reports allows clinicians to comprehend accurate results of their efforts and may increase sustainability [53]. The data reports need to be simple to understand, meaningful, and aligned with the ERAS goals. Champions found that sharing data reports helped to overcome skepticism and resistance [53]. The feedback to staff may take place during lunch and learns, reports, quick huddles, in-services, and meetings. Providing frequent and clear information and being transparent about the data will support the change [51]. Celebrating quick wins is vital to sustain users' motivation and keep going with the change [54]. The best short-term wins are those that are visible, positive, and align with the vision [55]. Achieving daily mobilization goals, discharging patients on targeted days, and increasing patients' satisfaction are examples of outcomes leading to

celebrations. Recognizing and perhaps even rewarding clinicians or teams who make those victories possible may also help in the sustainability, acceptance, and commitment of a change initiative [52].

It can be recommended that a few months after the implementation, all stakeholders meet to discuss the preliminary audit results. Patients' perspectives and data collections help guide the team to decide what needs to be modified in the care pathway. At the beginning of each year, the yearly ERAS objectives to be achieved can be communicated to the core team. During this meeting, a revision of the previous year's objectives is also presented along with underlying achievements, impending results, and ongoing improvements. Based on institutional policies and in light of new evidence, the multidisciplinary team should establish the frequency of revision to ensure best practices. Maintaining regular meetings with the ERAS multidisciplinary team will ensure engagement and motivation [18, 19]. Continuous feedback using audits, sending reminders, providing education sessions in small groups, and retaining a coordinator are all strategies to maintain the sustainability and effectiveness [19]. Sustainability is achieved when ERAS becomes the standard of care and is perceived as the norm in everyday practice [53, 56].

Conclusion

Implementing ERAS in a department requires planning, excellent communication skills, strong leadership, determination, and resources. Several facilitators and barriers are present throughout the creation, implementation, and sustainability. Disparity in surgical care is common, and the causes are multifactorial. This chapter has provided an overview of the different steps and change management strategies that may help in applying ERAS within a surgical department. It can also guide first-time users or to support organizations that wish to expand their ERAS program.

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60 Introducing Enhanced Recovery Programs into Practice: Lessons Learned from the ERAS® Society Implementation Program

Valérie Addor, Angie Balfour, and Olle Ljungqvist

Introduction

The enhanced recovery after surgery (ERAS®) program is an evidence-based protocol for the perioperative care of the patient undergoing major surgery developed by the ERAS® Society. This and similar enhanced recovery programs have been implemented in many surgical departments across a wide variety of specialties with varying degrees of success. ERAS® is a new way of working that is based on an evidence-based multimodal care program. ERAS has repeatedly demonstrated a reduction in length of hospital stay and a reduction in postoperative complications following elective surgery, which is clearly an attractive concept both for healthcare providers and for individual patients (see Chapters 40 through 58 for different specialties). However, despite the extensive and positive evidence base, the current literature highlights several potential barriers to ERAS implementation.

The Complexity of Perioperative Care

Because the evidence in the literature clearly shows that there are a multitude of choices along the patient's journey that can make a difference for the outcomes, they all need to be employed simultaneously. Some of the care elements involve preparation of the patient with medical, nutritional, and other preparative elements. Others involve the anesthesia and the choice of surgical technique, and others still involve the postoperative care where nursing becomes an absolute key aspect. Given this complexity of care elements, the multitude of medical decision-makers, and the large number and diversity of medical professionals involved, and not forgetting all the different locations where these care elements are provided, it is obvious that it is not an easy task to implement the perfect perioperative ERAS protocol.

Compliance to the ERAS elements has been reviewed throughout the literature [1], and it is clear that challenges still exist with various components of the ERAS® guidelines. Many of them are in the postoperative phase. One such element is early mobilization. Despite this activity being a cornerstone of postoperative nursing care, achieving dynamic mobilization (i.e., walking) can be particularly challenging to achieve for a variety of reasons, such as ward organization, advanced age, emergency surgery, traditional care, etc. Interestingly, emerging evidence shows that early mobilization may be one of the most important elements indicating successful and rapid recovery after surgery in ERAS [2].

Henrik Kehlet and the ERAS® Society have published numerous papers on ERAS and its forerunner fast-track surgery principles since the 1990s. In one of Kehlet's articles from 2008 [3], he described what he believed to be the key barriers to implementation, and these barriers resonated with many teams around the world:

- A lack of multidisciplinary collaboration (between surgeons, anesthetists, and surgical nurses)
- A lack of awareness of evidence-based data
- Failure to accept the published data
- A need for more data
- A lack of belief or buy-in from the institution
- External barriers such as time limitation and unavailability of outcome data
- Environmental barriers such as insufficient staff support and expertise

Professor Kehlet published once again in 2018 [4] and confirms that he is still "puzzled" as to why ERAS is still

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proving difficult to implement and sustain. He suggests that the main reasons for this are:

- Lack of knowledge
- Lack of acceptance
- Lack of ability
- Lack of wish to change
- Lack of clinical leadership

Tanious et al. [5] suggested that barriers to ERAS implementation can be split into five key components with several underlying issues contributing, again highlighting the complexity of the care process (Table 60.1).

Many teams and departments have attempted to implement ERAS programs over the last two decades—some of which have been successful but many have failed to sustain the program [6]. It is clear that a solid and rigorous structure must be in place, and support from the hospital management team should be sought to provide the support required to ensure that the dedicated team is able to successfully implement ERAS.

Table 60.1 Barriers to implementation of ERAS

Institutional component	Barrier description
Patient	Personal perspective on care factors such as readiness for discharge Large informational content per visit Lack of preoperative information Limited medical literacy
Medical professionals:	
Physicians	Resistance to change in practices Inadequate understanding, training, or support to undertake ERAS Perspective of successful outcomes, ERAS compliance without data support Variable attending-to-attending use of ERAS elements
Residents/house staff	Rapid turnover of residents on service Sporadic exposure to ERAS protocol lectures and inpatient practice
Nurses	Insufficient orientation to role in ERAS protocol Resistance to change in practices High patient-to-nurse ratios Rapid turnover of nurses Lack of knowledge regarding ERAS Insufficient ERAS education in colleges/universities
Hospital	Unavailability of funding for implementation Non-identifiable ERAS leadership, no local champion Suboptimal electronic medical record, lack of streamlined order sets Lack of formal implementation process adoption Absence of data collection, auditing system with continuous feedback

Adapted with permission from Tanious et al. [5]

In the United Kingdom, the Department of Health commissioned the Enhanced Recovery Partnership Programme (ERPP) to support the National Health Service (NHS) in introducing the principles presented by the ERAS group [7]. Several leading units with well-functioning enhanced recovery programs were engaged to teach others across the country during lectures and training sessions. Protocols of the care elements were distributed, and an audit system was employed to follow changes in practice and outcomes. The program was ambitious by involving not only colorectal surgery, which had been the starting point for ERAS, but also major urology, gynecology, and orthopedics. The results of this large effort were positive, with approximately 1-day reduction in hospital stay for most of the protocols. Unfortunately, this government program was stopped after a few years, so it is difficult to assess the sustainability of this program.

Another approach was taken in the Netherlands, where members of the ERAS Study group joined forces with Central Accompagnement Organization (CBO—the Dutch Institute for Health Care Improvement) to run a series of implementation programs [8]. These programs in colonic resections proved to be even more successful, with an average reduction in stay by 3 days. A major difference between the two programs was the introduction of professional coaching of the ERAS teams that were installed in each of the units under training. These teams were trained to institute changes according to a structured breakthrough methodology. Again, however, the program was not followed up in any orderly manner and a few years later showed that a majority of the units had fallen back in their compliance with the protocol and showed a longer length of stay. This occurred despite the introduction of minimally invasive surgical techniques during that time, which would be assumed to have resulted in a further reduction in stay. From these and other experiences also from North America [9–11], it is clear that several of the hurdles of implementation can be overcome once they are identified and addressed properly.

ERAS® Implementation Program (EIP)

The pioneering groups in protocols implementation have shown how difficult it is to implement a protocol and maintain the results in a long-term work [12]. The success and sustainability of a program such as ERAS depends on how it has been implemented in surgical departments [2]. The purpose of the ERAS® Implementation Program (EIP) is to give the participants theoretical as well as practical knowledge on how to implement and sustain work using ERAS principles.

In order to describe the EIP, the topic will be separated into several key areas for consideration.

Framework and Contents of the ERAS® Society Implementation Program

The ERAS® Society Implementation Program (EIP) is run over a series of four seminars where several hospitals send multidisciplinary and multiprofessional teams for training. One of the keys to a successful EIP is in the structure and progressiveness of the implementation in the different seminars and the expertise of the coaches that are available to assist throughout the entire process. The ERAS® Society program consists of four training seminars (three of them face-to-face with all teams meeting up and one as an online reporting seminar with all teams) and three action periods that take place between each seminar (Fig. 60.1). An EIP is approximately 8 to 10 months in duration. During the EIP, ERAS® Society appointed clinical experts support the ERAS novice team in training. The overarching goal for the teams is to learn how to make changes and to work with audit to control the changes and their care processes and outcomes.

Philosophy and Background of ERAS

The ERAS team learns about the importance of working as a team around the patient and the role of the treatments and their interactions that build the ERAS concept. It is the basic understanding that each profession and each element has a role to play, what it is, and how it impacts and fits the overall care process. This is how ERAS helps each professional to improve the quality of their own care. This knowledge is taught to the teams, and they use these insights to implement evidence-based practice and to educate patients and staff. The ERAS team also analyzes all the care data and monitors processes and results using the ERAS® Interactive Audit System. During the training, the teams will experience the value of knowing the details of care and to use that insight to secure best care processes.

The ERAS Multidisciplinary Team

Constructing a multidisciplinary ERAS team with strong leadership is essential to implement ERAS [13]. It is crucial to attract and involve the people with local leadership and/or

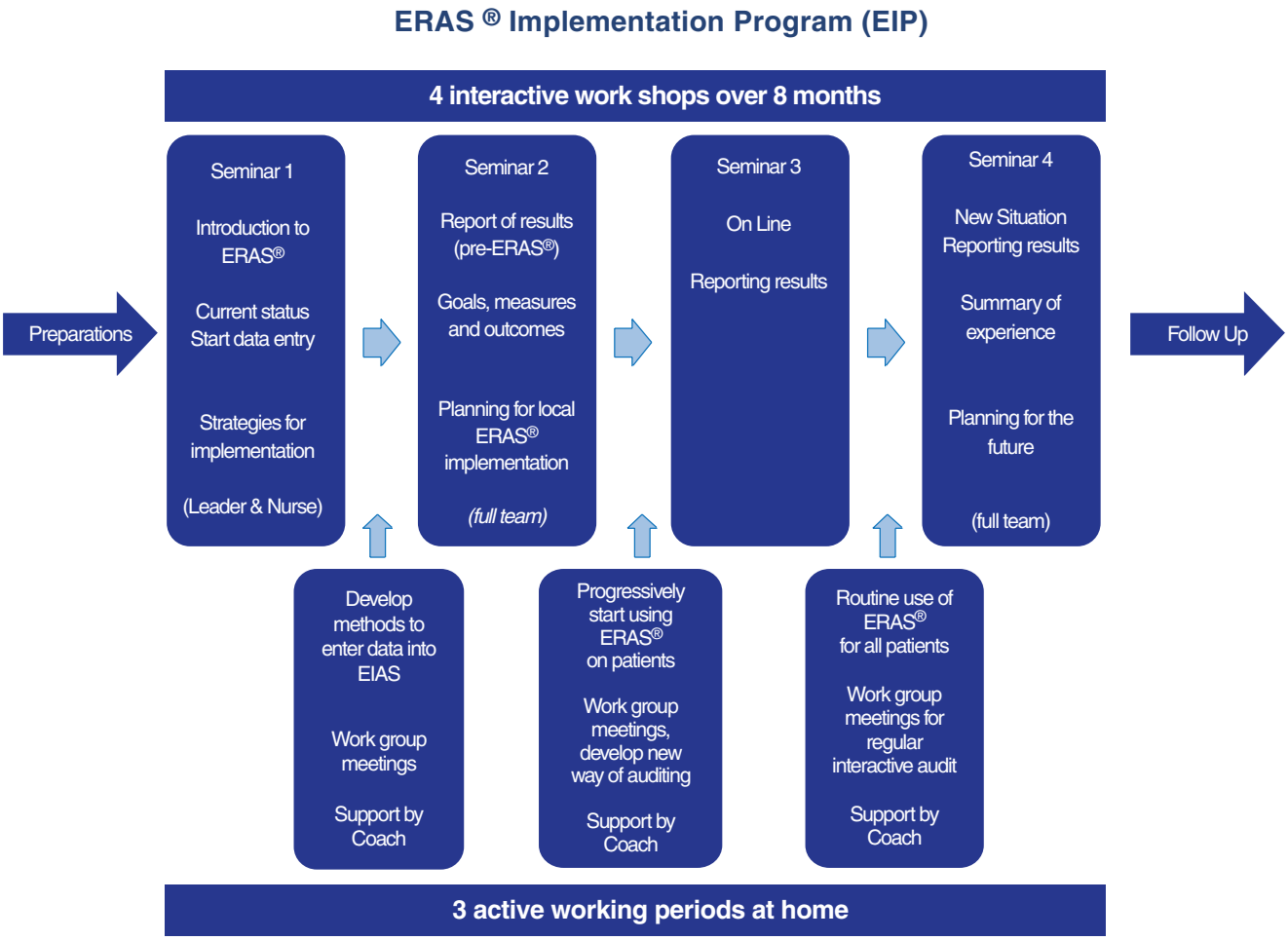

Fig. 60.1 The training of the ERAS team covers different sections. (The figure is used by permission of Encare.net. https://www.encare.net/healthcare-professionals/products-and-services/eras-implementation-program-eip)

influence to take part and lead the ERAS implementation. The basic core for an ERAS team consists of one or two surgeons, one or two anesthetists, an ERAS coordinator (often a nurse), a hospital management representative, and a senior nurse from each of the clinical areas (outpatient clinic, high-dependency unit [HDU]/post-op care, and the ward). A surgeon with influence and full support from the department head should lead the EIP team. Similarly, positioned anesthetists would be in the team. The ERAS coordinator is responsible for the effective and efficient implementation, which involves several key components such as creation of documentation (clinical pathways, patient education material) data collection, education for both patients and nursing staff, leading ERAS team meetings, and disseminating results. They should have direct access to the lead surgeon and manager overseeing ERAS implementation to ensure a prompt response to any emerging problems.

Importance of Data Collection and Use of the ERAS® Interactive Audit System (EIAS)

Martin et al. [14] demonstrated that implementing an enhanced recovery program without real-time result tracking often fails. During the ERAS® Implementation Program, teams start to use the ERAS® Interactive Audit System analysis tool. This will allow them to, in most cases for the first time, track their own results as well as the care practice behind their outcomes. In the implementation of ERAS, the use of EIAS is essential. This allows everyone to see what is actually happening during the care processes. It is only with this insight that the correct changes that are needed can be addressed.

It is therefore essential to collect accurate and reliable data in order to analyze them and make the necessary corrections to improve the quality of patient care and sustain the results. This is a key aspect of the implementation program.

Change Management

With the insights of where the gaps are and where changes are needed for implementing ERAS in the unit, the ERAS team learns how to use methods for the change of practice from the clinical experts. The teams are trained to apply the concept of the Deming wheel [15] or so-called PDCA (plan-do-check-act) or PDSA (plan-do-study-act) cycle, which allows monitoring the evolution of the implementation through four phases (Fig. 60.2).

During the entire EIP, the importance of multidisciplinary team working, the implementation organization, and regular and continual evaluation is emphasized throughout. The focus is also on value of constant support from the ERAS team to all colleagues performing the care on a daily basis. At the end of the 8–10-month-long EIP, the goal is that participants of the ERAS teams are able to maintain the new practices in the long-term work and have a readiness to make the next change as it arises. They will also have developed a routine to communicate with the rest of their colleagues and to the management team about the current state of the care and the results that have been achieved.

The organization of the implementation of ERAS requires a clear definition of the roles and objectives of each team member. The aim is to use a common language to ensure successful implementation across traditional nursing and

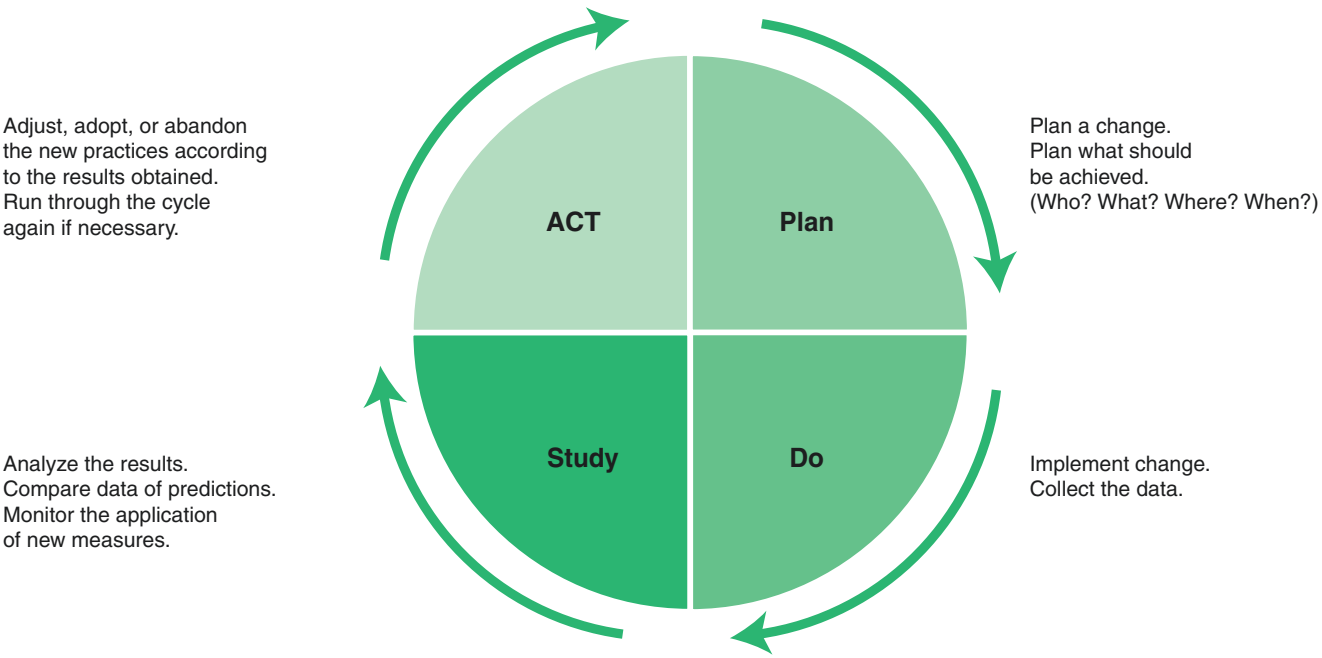

Fig. 60.2 Four phases of a Deming wheel

medical boundaries. Meetings should be held on a regular basis, initially every week and then at least once a month, with mandatory attendance of all the ERAS team members, especially during implementation.

Feedback on the Clinical Experience Linked to the Protocol

ERAS protocols have been established based on evidence-based practice as reviewed and updated by the ERAS® Society guidelines groups. During the EIP, the clinical experts in ERAS training the teams share their own daily experiences with novice teams during and in-between the seminars. Practical subjects such as the organization of pre-operative information, fluid management, or data collection require the cooperation of different stakeholders and necessitate review of the functionality of the team. Implementing ERAS can often create a need for reorganization of nursing care in a department when introducing new features, such as weighing patients every day or helping them achieve the required mobilization goals.

Sustainability of Results

After the completion of the EIP, there is a risk that the ERAS team will settle down with its success and relax its attention on the application of ERAS measures and the recording of the data necessary to monitor the results. The turnover of nursing and medical teams [15] presents another risk of failure in the long term, unless new appointees are trained and understand the application of ERAS principles. Francis et al. [13] demonstrated that to sustain the results obtained at the end of EIP, it is necessary to maintain continuous training in small groups, continuous data collection, and critical analysis to provide regular feedback to the teams as well as to all co-workers and a readiness to improve practices where necessary.

Internal Communication for the Success of ERAS

During the implementation of ERAS, communication is a key factor. The team needs to secure internal open and transparent communication and to ensure that the same message is delivered from the team to all co-workers. The team also needs to communicate results from the audit to all collaborators along the patient journey at regular intervals. This is the only way to secure the adherence to the protocol by the medical and nursing teams and all the care partners involved in the ERAS protocol. The role of information—describing what is to be changed, why it is to happen, and how it will be done—is particularly crucial during the implementation period. This is the time to build the communication plan and to set it into action. Informing about the objectives and expected benefits—the implications for the patient, the surgeon, the anesthetist, and the caregivers—gives meaning to the new practices. This should be followed by disseminating the results obtained at the end of the implementation to show the effectiveness and/or the failure of compliance to the various ERAS elements. This helps form the next steps to be taken in a continuous mode of improvement. Reporting to hospital management is equally important as it helps reaffirm the financial gains and secure ongoing support for personnel and resources necessary to sustain ERAS. It is also quite common that the implementation of ERAS in one specialty leads to the urge from management to also use the same methodology for other specialties.

Key Factors for Success

The difficulties encountered during an EIP can be various in nature: financial, support from leadership, resources for clinical staff, equipment, logistics, etc. Sometimes it is related to the situation of the hospital itself and its personnel, lack of leadership for the team, change of personnel, shortage of staff, and lack of dedication. To enter an ERAS® Society-run EIP, it has been insisted on that an agreement from the budget holders is in place to secure the funding for the team during the training. Without financial support from hospital management, there is no guarantee of the presence of an ERAS coordinator or nurse and dedicated time for the ERAS team. These two fundamental issues need to be supported to ensure a successful and worthwhile implementation process. The teams need logistical support to organize the ERAS-dedicated nursing interactions with the patients and assistance to produce patient documentation. A constant support from the department and nursing heads, as well as any leadership in the hierarchy and hospital management, is one of the key factors for the successful implementation of ERAS. The support of the novice teams by ERAS experts throughout the implementation is another key element for their success. The availability to answer or give practical solutions regarding clinical or organizational preoccupations is an important part of the program. Communication, understanding, and respect for each other's roles inside the ERAS team are other key points for the successful implementation of ERAS. This team support makes it easier to face the difficulties encountered and find joint solutions validated by the whole team.

The sustainability of an established ERAS program is an ongoing challenge and requires the dedication and commitment of the ERAS team and its tasks, which in turn places demands on financial and educational resources [7]. Repeated training sessions for new personnel and the presence and availability of the ERAS nurse coordinator must be supported and involved in the different stages of perioperative patient care. Maintaining regular ERAS team meetings but also holding regular meeting for all personnel involved is a

key factor to maintaining compliance after implementation. Regular feedback using the audit and local data during the regular scheduled meetings should be shared with every working group involved: nurses, allied healthcare professionals, and doctors.

Results and Outcomes from Implementation of ERAS

Reports from the literature show that employing more of the elements recommended in the ERAS guidelines also results in better outcomes [16, 17]. What is also clear from the literature is that the standardized training using methodology combining the clinical insights of the producers of the ERAS protocols alongside the expertise in change management in healthcare has proven very beneficial [18, 19]. This was already demonstrated in the piloting experiences from the Netherlands and has later been shown to hold true in other countries as well [8]. In general, the EIP training programs will help units to gain insights about their practice, and in seeing this they will also understand why they have certain problems. Many units find that during the EIP, they manage to increase their compliance to the protocol significantly, and in doing more things according to the literature, they also get the clinical results. It is not uncommon to reduce length of stay by 30% or more. Behind these improvements is often a similarly large reduction in complications.

Conclusion

Implementation of ERAS has tremendous positive impact on outcomes for the patients and on the cost of care. This is a true win (patients)-win (caregivers)-win (healthcare providers) situation [20]. The implementation of an ERAS program is facilitated by a solid and rigorous structure. The construction of a dedicated local ERAS team, supported by the hospital's management hierarchy, enables the necessary organization to implement the protocol, to sustain, and to further develop ERAS locally. The use of data collected and analyzed makes it possible to target improvements to where it needs to be to raise the quality of care for patients. The application of these elements guarantees the successful implementation of an ERAS program.

The EIP team conducts regular education sessions throughout the implementation process, and a designated team of ERAS coaches is assigned to work with the clinical teams. Buy-in is an essential component to a successful implementation, and this must include the managers and finance team as they need to have an overall understanding of the benefits an ERAS program can provide to the organization as well as the patients.

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Enhanced Recovery After Surgery – Making the Business Case: Economics – The Alberta Experience

61

Tracy Wasylak, Kevin Osiowy, and Anderson Chuck

Introduction

Decision-makers strive to reduce health-care costs, improve capacity, and get the best value for every dollar spent in health care. There is ample evidence reported in the literature of health systems achieving major gains, clinically and economically, by implementing a single guideline that modifies perioperative decisions (preoperative, intraoperative, and postoperative). These guidelines have potential to transform perioperative management of ALL surgical patients; however, there is limited documentation of the spread and scale of enhanced recovery after surgery (ERAS) protocols across clinical sites and health systems. Similarly, little information is available about the potential impact on surgical programs and health systems of implementing multiple guidelines across multiple sites. Recently, the published literature has shown the value of ERAS guidelines from an economic perspective and looked at the return on investment of ERAS programs. More can be done to evaluate and expand the economic value—within hospitals and post discharge. Building a case for widespread implementation of ERAS guidelines, and supporting change within health systems, requires a focused approach, a clear implementation and evaluation framework, and a robust business case that conveys the potential impact. These elements are essential to enable evidence-based decision-making about transformational investments.

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The Evidence for ERAS

Improving the quality and performance of health care is one of the main challenges facing health systems and governments worldwide. International guidelines for enhanced recovery after surgery (ERAS) have existed for 15 years with well-documented evidence of improvements for individual patients and specific surgical populations [1–4]. ERAS guidelines outline a series of evidence-informed practices (preoperative, intraoperative, and postoperative) aimed at mitigating adverse effects of surgery using a team-based approach. These practices have been associated with accelerated recovery, resulting in reduced complications and hospital lengths of stay (LOS), fewer readmissions, improved patient experience, and no associated increases in health services utilization [3, 5–8].

There is ample evidence that ERAS protocols improve patient care and experience and provide economic value to health systems. Across the globe, health systems are adopting a Quadruple Aim approach to improve system performance (patient and provider satisfaction, improved clinical outcomes, and economic value for the health system). Yet, even more health systems would benefit if they adopted ERAS programs within their hospitals [9]. This surgical transformation has been shown to significantly improve system performance—clinically and financially—for almost every major surgical procedure in many centers around the world [10].

Despite this success, uptake is slow, and we know there are millions more surgical patients worldwide who could benefit from ERAS programs. While this observation is noted, it is unclear what the barriers are to advancing uptake and is, therefore, a potential area for further inquiry and research. The evidence does show that by adopting ERAS guidelines, decision-makers can affect positive individual and surgical population outcomes while reducing complications and per-unit costs and freeing up capacity through reduced lengths of stay, readmissions, and overall health services utilization. The evidence points to a health system's

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potential to magnify these benefits by systematically implementing the existing research findings and looking at methods to spread and scale ERAS protocols to all surgical patients.

Large-Scale Implementation of Multiple ERAS Guidelines

Few health systems have attempted to implement multiple guidelines system-wide. The United Kingdom's Enhanced Recovery Partnership Programme (ERPP) included multiple guidelines across multiple sites with good outcomes for surgical patients and the system itself [11]. They describe a system-wide attempt to implement multiple guidelines for several surgical disciplines including orthopedic, urology, colorectal, and gynecologic procedures. Although they did see a positive impact, the authors concluded that a stringent implementation process should be in place to ensure compliance with the guidelines beyond the implementation phase [11]. The Netherlands implemented the ERAS International© Society Colorectal Guideline, using what developed into the ERAS® Society Implementation Program, across 33 sites with results similar to those reported by others in the literature [11, 12]. The ERAS® Society's implementation approach is modeled after the Institute for Healthcare Improvement's (IHI) learning collaborative methodology and assists teams with education, data, and process improvements to guide the ERAS implementation at the site [11, 13].

In Canada, in the Province of Alberta, Alberta Health Services (AHS) has implemented multiple ERAS® Society guidelines across nine major sites and nine program areas. AHS adopted the ERAS® Society approach by using the evidence-based guidelines and implementation plans based on IHI methodology and adopting the ERAS International© Society's Interactive Audit System (EIAS) for data collection, audit, and feedback. Results from Alberta have been very positive and show value across all Quadruple Aim goals: patient and provider satisfaction, improved clinical outcomes, and economic value for the health system [3, 5, 14, 15].

Barriers and Enablers of ERAS Implementation

Gramlich et al. studied the implementation of ERAS protocols across six colorectal sites to better understand the barriers and enablers to implementation and to maximize guideline compliance [3]. High compliance was identified as being important to achieving results, especially when considering the use of multiple guidelines within and across surgical centers [16, 17]. They used two frameworks to guide their review: (1) the Theoretical Domains Framework (TDF) and (2) the Quality Enhancement Research Initiative (QUERI) Framework [18, 19]. The team applied rigorous methods for implementation that not only led to behavior change and helped sustain that change but also has supported the development of spread and scale opportunities within Alberta [3, 20–22].

Mapping barriers and facilitators across the different domains—patient, provider, and system—provides insight into the change strategies that might best drive compliance [3]. McLeod et al. identified four key ingredients for successful guideline adoption: (1) clinical champions, (2) good communication and collaboration, (3) organizational management, and (4) use of audit and feedback processes and standardization of orders [23]. This research is in keeping with work done by Pearsall et al. who looked at barriers and facilitators to ERAS implementation across four hospital sites [17]. They identified barriers to implementation that included limited financial and human resources to ensure audit and feedback, absence of change management strategies and supports for standardization (e.g., standardized order sets), poor communication and collaboration, and absence of clinician or organizational champions. These elements were considered essential to affect change. Standardized patient education and family involvement in the process were also identified as important components. This information is critical to successfully spread and scale ERAS guidelines as implementation is complex and typically requires multiple strategies to achieve the objectives. Unfortunately, there is no "one-size-fits-all" approach, and it is important to understand what is required to change behavior at the provider level, site level, and system level. For example, customized audit and feedback of individual performance based on compliance with ERAS practices and protocols might be helpful at a provider level. At the site level, the approach (e.g., standardized fasting guidelines as part of preadmission process) may be different than what is required at the system level (e.g., standardized patient education materials for all sites and standardized education for all staff across the health system).

Monitoring Compliance and Outcomes

Audit and feedback mechanisms are an important component of the implementation program as they provide a means of regularly evaluating outcomes (e.g., LOS, surgical complications, and patient-reported outcome measures) and compliance with ERAS guidelines [3]. While some programs have adopted the ERAS® Society Interactive Audit System (EIAS), several methods of measuring ERAS

impact have been used worldwide with little evidence to suggest one method is superior. The essential ingredient to successful implementation is measurement and feedback that provides meaningful data to measure improvements in practice and key outcomes. Moreover, it is necessary to clearly outline those planned improvements in the business case that are proposed to decision-makers. Measurement and feedback are important as tools to manage both the individual patient progress and team progress; the EIAS system was designed to provide near-real-time feedback to clinicians and teams. When instituting the EIAS, teams could use the feedback to manage individual patient progress and to better understand where the team had achieved compliance with the ERAS elements. Studies have shown that high levels of compliance with ERAS guidelines provide better results [16] and can help sustain the clinical and economic gains achieved. It may be surprising for decision-makers that a sum of relatively simple perioperative measures, such as early mobilization and oral nutrition, impacts patient outcomes to the extent that has been documented. However, these results highlight the importance of engaging health-care providers in refining and implementing standards and processes that lead to quality improvements and better value over time [24–26].

Developing a Model for Spread and Scale

In evaluating barriers and facilitators of ERAS implementation, Gramlich et al. developed a model to spread and scale ERAS protocols [3]. The model suggests that strategies to achieve compliance with ERAS guidelines can be applied across many surgical areas to support widespread implementation. The model includes four elements (Fig. 61.1):

- Nutrition
- Mobilization
- Fluid management—including modern fasting guidelines and carbohydrate loading
- Pain and symptom control

The model highlights patient-focused information and education as an important enabler to successful spread and scale. This finding is consistent with several studies that have

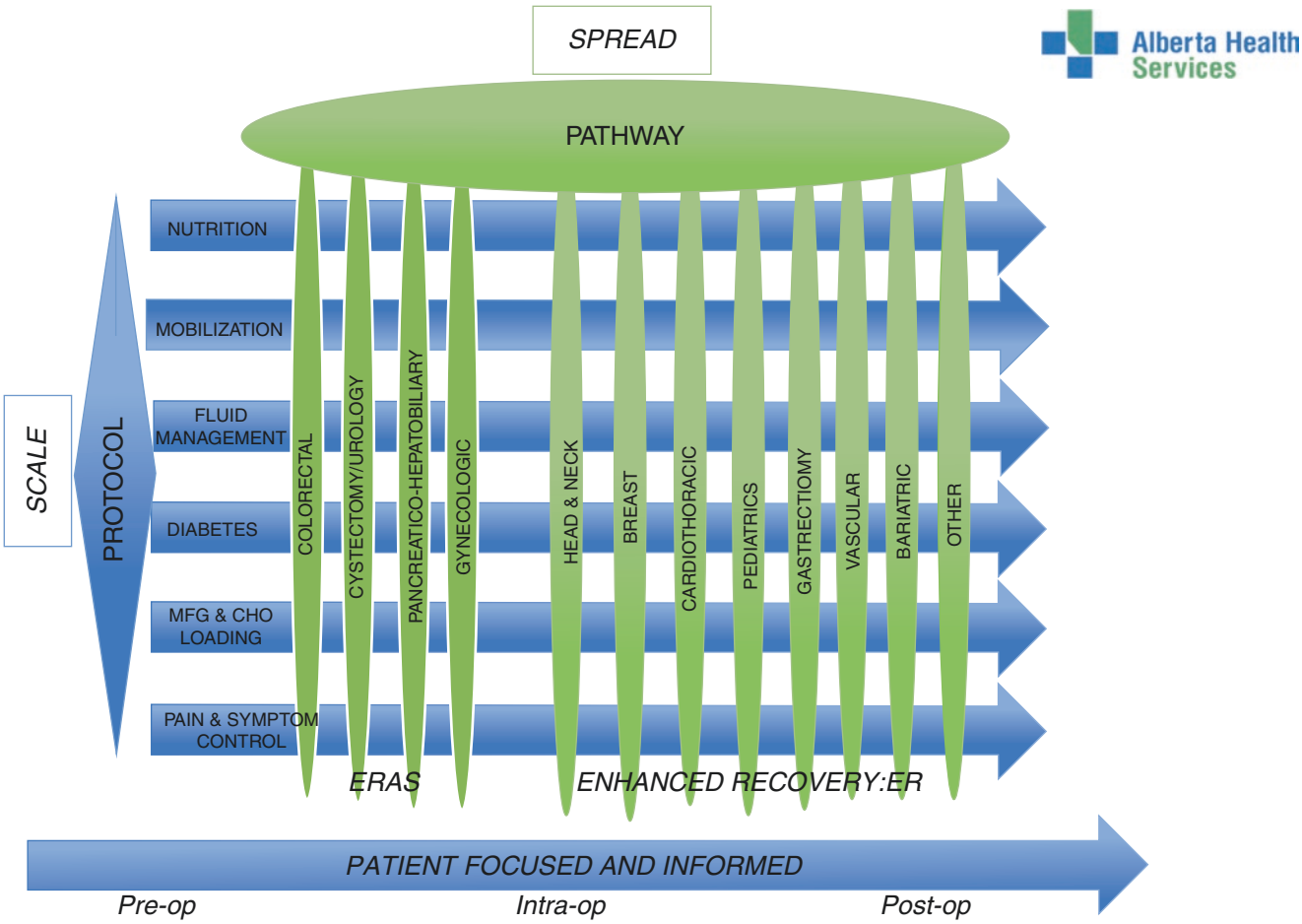

Fig. 61.1 Model for spread and scale of ERAS protocols

reported the need for better patient and family education and involvement—especially in the preoperative and postoperative phases of the surgical experience. However, there is little evidence that these changes have made their way into clinical systems. Few studies have reported any patient-reported outcomes, and this is viewed as a shortcoming of the ERAS evaluation. Patient-centered care is an important concept among health providers, and most health systems monitor patient-reported outcomes as part of their quality management systems. The absence of patient-reported outcomes is currently a gap in the ERAS literature and evaluation tools and an area for future research, especially for recovery beyond the postoperative stay [17, 27].

Considering and Preparing a Business Case for ERAS Implementation

Given the initial investment needed to successfully implement an ERAS program (i.e., to develop evidence-based guidelines, an implementation approach, and a measurement system to ensure audit and feedback), there is value in providing a robust business case for managers and decision-makers. The business case must clearly address the clinical advantages and improvements for patients and clinicians as well as the metrics and value proposition for the site. The challenge is often that the metrics important to decision-makers differ from (or need to be expressed differently than) the metrics important to clinicians. The ability to build a case that clearly conveys the value proposition to both parties is critical to ERAS implementation.

To demonstrate impact while describing the value to the organization, the business case must consider the patient, providers, organization, and the overall health system [3]. However, even when evidence is expressed in economic terms, health administrators have found it difficult to relate these gains to real system savings. Most of these gains are described in terms of freed-up capacity (bed days saved), improved productivity (decreased readmissions), improved safety (reduced complications), and cost-effectiveness (health system savings and greater value for each dollar invested).

Given the capacity strains and economic pressures that most institutions experience, gains in capacity are typically short-lived because freed-up surgical inpatient beds are rapidly filled by the ever-increasing demand of other programs and services. This masks the impact of ERAS, making it appear somewhat theoretical; without the ability to close surgical beds, the clinical gains do not necessarily translate into real cash savings for the system. So for many decision-makers (especially those with relatively fixed, global budgets), the case for investing in ERAS may be more difficult to justify from a financial perspective despite the positive clinical gains.

Making the case for more investment into ERAS is challenging, and it can help to take a broad and long-term view. As more complex patients are treated in hospitals with surgery, and the increasing cost to add more physical capacity is prohibitive, administrators must seek innovative solutions that can advance productivity and capacity gains within existing hospital footprints. While innovative solutions (such as the ERAS ingredients) cannot be expected to reduce total health-care expenditures in absolute terms, they do, however, have the potential to free up a significant amount of capacity that may enable health systems to significantly increase surgical throughput. Doing so results in the provision of more timely hospital service to other patient populations. The potential to significantly increase patient throughput with existing hospital capacity could be realized by deploying the innovative solution at scale. For instance, by applying the key ERAS ingredients to all surgical patients at a particular hospital, it may be possible to provide decision-makers with a credible quantitative forecast that shows that more patients can be treated within the existing hospital capacity at a fraction of the cost of the next-best (though economically unlikely) alternative—that is, of adding more physical capacity. Clinical appropriateness (using evidence-based guidelines) and improving care efficiency (reducing unwarranted variation and cost) are fundamental drivers to transformational change and to becoming a high-performing health system—something that the case for ERAS has proven.

Building the Case for ERAS in Alberta

Alberta Health Services (AHS) is Canada's first province-wide, fully integrated health system. Created in 2008, AHS is responsible for delivering health services to more than 4 million people. In June 2012, AHS introduced Strategic Clinical Networks™ (SCNs), which are collaborative teams of clinicians, researchers, and stakeholders to advance innovation across the province's health system. Specifically, their mandate and goals are to achieve best outcomes; seek greatest value for money; and engage clinicians, patients, and health providers in all aspects of the work. SCNs are led by clinicians, driven by clinical needs, based on measurement and best evidence, and supported by research expertise, infrastructure, quality improvement, and analytic resources [28].

Quantifying the value or return on investment (ROI) of quality and patient safety initiatives is part of the SCN mandate as a means of becoming a higher-performing health system. In Alberta, more than 275,000 surgical procedures are performed annually in 58 surgical facilities, with 16 of these performing 85% of major surgical procedures in the province [5, 15, 29]. Given the mandate of the SCNs, the diabetes, obesity and nutrition, and the surgery SCNs built a business case and demonstration project to implement the ERAS® Society's international guidelines [24]. Since 2013,

AHS has implemented multiple ERAS guidelines at nine sites and across nine program areas. Clinical and economic evaluations have shown improvements associated with accelerated recovery, including reduced complications, shorter length of stays, improved patient experience, and reduced health service utilization [5, 14, 15]. Alberta showed that the health system savings were estimated at $2,290,000 (range $1,191,000–$3,391,000); after factoring the project costs of implementing ERAS, the net cost savings of ERAS was $1768 (range from $920 to $2619) per patient. In terms of the value proposition associated with this investment, the analysis demonstrated that every $1 invested in ERAS programs would bring about $4 in value to the system [5].

For AHS, maximizing value is a fundamental principle to creating high performance in the health system. Specifically, AHS has described organizational value as a function of:

- Quality, safety, and outcomes
- Process improvements
- Timing of expected benefits
- Budget/financial impact
- System readiness
- Value for money

Therefore, to build the business case for ERAS, these six dimensions must be described and, where possible, quantified to best understand the overall value that a particular innovation contributes to the system. As ERAS results in a lower cost per patient (quality, safety, and outcomes), it is logical to assume that from a spread and scale perspective, the more patients enrolled, the more organizational value will be created. Important factors for ERAS long-term success are changes in management of care processes and time investment to form multidisciplinary and interprofessional ERAS teams along with the use of continuous audit and feedback.

Building the case for ERAS started by developing a change proposal that focused on "doing the right thing" by identifying and proposing an approach that addressed the quantifiable gap in health system performance. From there, the SCNs developed a high-quality operational and financial plan to make the solution work in practice. To achieve this, the team developed a framework (with support from AHS's innovation and research management and finance teams) that provides a comprehensive plan that supported both clinical implementation and decision-maker requirements.

The framework (Fig. 61.2) consists of five components:

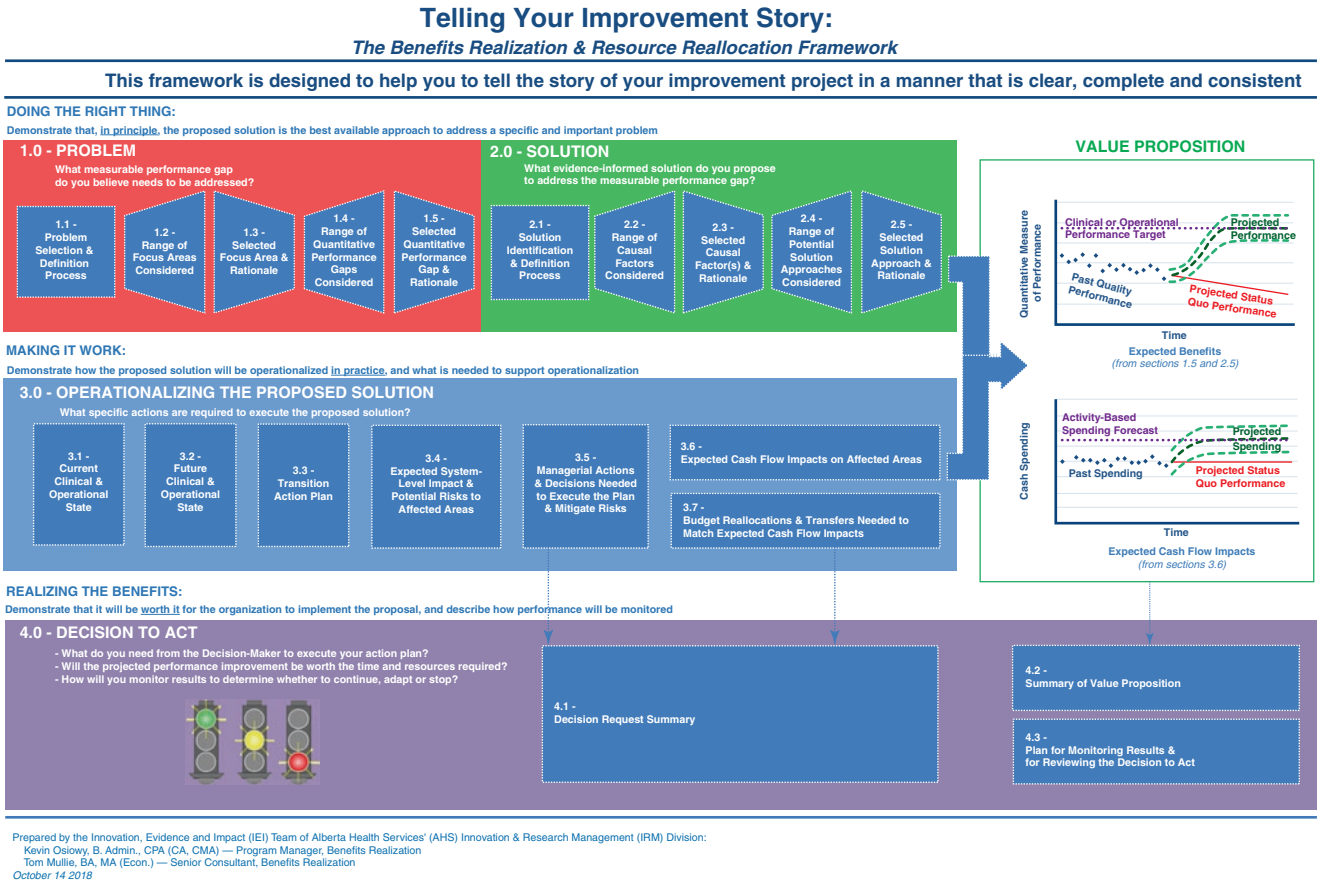

Fig. 61.2 Benefits realization and resource reallocation framework

Step 1. *Problem Identification*—Identify the specific problem to focus on, defined as the gap between current performance and potential performance. Use a quantifiable measure that relates to the organization's goals and priorities (e.g., Quadruple Aim).

Step 2. *Option Analysis*—Review and select a solution from a range of options. Evaluate the options based on clinical input and research findings. The analysis should include a well-supported estimate of the magnitude of the potential impact in terms of the quantifiable measure (identified in Step 1) and be based on evidence in the literature (e.g., ERAS international guidelines).

Step 3. *Preliminary Projections*—Use available data to complete a preliminary forecast of projected performance improvement, showing how the gap between current and potential performance (from Step 1) will be reduced. In Alberta, the findings from the UK study provided options (Step 2) and data from which to estimate the order of magnitude that could be achieved with full-system implementation. This data was used to estimate potential benefit that would accrue to Alberta Health Services (AHS), based on Alberta surgical volumes.

Step 4. *Operational and Financial Impact Assessment (OFIA)*—Evaluate the anticipated impacts of implementing the solution on the health-care system by conducting a detailed OFIA. The OFIA should be informed by consultation with expert representatives of sites, services, and units that would be potentially affected by the implementation. The OFIA should also outline plans to mitigate any adverse impacts on other areas of the system.

Step 5. *Business Case Development*—Describe the potential benefits and costs of implementation (i.e., the value proposition), include a clear recommendation, and request a decision. The business case should also summarize all managerial actions (e.g., financial transfers, policy changes, communications support) necessary to support implementation and include a plan to review the implementation decision at a defined time and according to the project's performance (based on quantitative measures defined in the business case).

A business case for transformational investments must provide clear and complete information about the project for decision-makers at a level of detail that enables them to understand exactly (1) what the project offers in terms of progress toward their goals and (2) what is needed in terms of system resources to deliver on that promise.

ERAS Implementation to Date in Alberta

As mentioned, AHS has implemented ERAS guidelines at nine sites in nine program areas. Alberta's three major teaching hospitals have adopted multiple guidelines in several surgical program areas, including orthopedics, gynecology, liver, major head and neck oncology, colorectal, pancreas, cystectomy, and breast reconstruction. Several of the surgeons in Alberta have been part of, or have led the development and testing of, the international guidelines [15, 30–33], and there are plans underway for further guideline development.

The AHS investment in ERAS has been a direct result of having a clear and compelling case for change and a comprehensive implementation plan. The implementation plan was built as a result of research conducted in Alberta to understand the barriers and facilitators of multiple guideline implementations. This research was supported by a Partnership for Research and Innovation in the Health System (PRIHS) grant. Important ingredients that contributed to success included the surgeon, anesthesia and local administrative champions, standardized approaches for education and implementation, and a robust audit and feedback capability. A systems perspective and structured approach to communications across multiple sites was also considered critical to the project's success [3, 15].

In building the case for investment in ERAS, there is compelling evidence published on the value of single-protocol implementation. However, if there is an inability to utilize the freed capacity/resources as the fuel to sustain continued transformative change, then, unfortunately over time, compliance with the guidelines can be expected to deteriorate. In an environment of increasing scarcity and scrutiny of health-care budgets, non-compliance can occur if efficiency gains are completely utilized toward other priorities during corporate budgeting processes. This ultimately can cause increased pressure, staff workload, change fatigue, and operational risk, and it also may inhibit quality improvement. An approach that may help find the balance between fueling continued transformative change and other organizational priorities is adopting a benefits sharing approach.

Incenting Change and Quality Improvement Through Benefit Sharing

In Alberta, the Institute for Health Economics (IHE) conducted a rapid review to understand how health systems were building incentives and policy to recognize and reward quality improvement efforts [34]. The review revealed two main types of incentives: those described as "gain sharing" and

those described as "shared savings." Gain sharing is defined as an arrangement with employees where the organization shares a portion of the savings (cost reductions) attributable to the efforts of those employees and where the rewards are allocated back to teams or individuals based on the improvements. Gain sharing includes concepts such as pay-for-performance, global payments, bundled payments, and pay-for-coordination payments geared at promoting provider accountability [34]. Many of these efforts have been introduced across several health systems within European countries, with limited published literature on the outcomes/outputs of these efforts.

With the recently adopted *Affordable Care Act* in the United States, accountable care organizations (ACOs) and payment schemes to reward better outcomes have proliferated. The major risks and benefits associated with gain-sharing methods include complicated payment schemes, difficulty with the attribution of outcomes, and potential conflicts with providing monetary payback to individual providers. Gain-sharing programs require measurable and clearly stated goals, transparent data sharing among stakeholders, and safeguards against inappropriate referrals or reductions in care quality [34].

Alternatively, shared savings (also referred to as benefits sharing) is described as an approach that links an organizations' planning and budgeting process to employee-created, operation-led performance improvements. There are two types:

- *One-sided (upside) risk model*: Providers (usually hospitals or physician practices) would provide decision-makers with specific plans/proposals that would have them retain within their clinical business unit some predefined portion (either a specific amount or a particular proportion) of planned operational or financial performance gains in the event that those planned gains were actually realized. The proposal would outline how the business unit would be able to fuel further performance improvements (i.e., to create further value) as a direct result of retaining these gains. While business units would be allowed to propose the retention of some of the planned gains actually realized, they would not, however, be subject to any sanctions or penalties in the event that they were not able to achieve planned performance gains.
- *Two-sided (upside and downside) risk model*: Under this type of arrangement, providers would be able to provide decision-makers with specific plans/proposals that would have them retain within their clinical business unit some predetermined portion of planned gains to fuel further performance improvements. Similar to the one-sided (upside) risk model discussed above, providers would be allowed to propose the retention of some of the planned gains actually realized. Unlike the one-sided (upside) risk model, however, the two-sided risk model would make the provider more accountable for the realization of planned results in that their proposal would be expected to specify the mechanism by which the decision-maker would recover a portion of the investment in the event that actual, measurable performance improvement was materially less than planned [34].

In the IHE review, shared savings are described as models that "encourage collaboration among providers to reduce the use of health services and improve quality in a population over time. This reimbursement strategy is well suited to the ethos of ACOs because it incentivizes providers to develop effective primary care prevention and population health management strategies, with the aim of decreasing utilization by avoiding hospital admissions, reducing readmissions, and improving care coordination" [34]. Because of its focus on clinical improvement, the shared savings approach (especially the balanced two-sided risk model, above) encourages providers to "do the right thing" and then provides the financing mechanism to "make it work."

There is little published literature on the use of incentives to drive quality improvements in health systems. The largest number of studies comes from the United States as a result of the policy changes in their system related to the *Affordable Care Act*. "In Canada there is no ACO equivalent, and it is rare for front-line workers to be given responsibility for initiating change or to be compensated directly for such efforts [35]. Although the highly regulated nature of Canada's provincial health systems is a potential barrier to gain sharing and shared savings initiatives, there are examples in both Ontario and Alberta Health Services that are experimenting with these approaches" [34].

Alberta Health Services has recently adopted a benefit-sharing strategy as part of its annual resource allocation and budgeting process for the province. Under the new approach, clinical teams that propose the adoption of innovative solutions to drive measurable improvements can apply for benefits sharing. Under benefits sharing, benefits are not automatically taken back into the corporate budgeting process and used for other organizational purposes, but rather are a source of capacity or resources (i.e., fuel) to enable clinical programs across AHS (including the program leading the innovation) to reinvest some or all of those measured gains to help them improve organizational value (i.e., manage their business) by enabling them to manage priority clinical pressures and improve quality or patient outcomes. AHS notes that efficiency gains are those that are predominantly nonmonetary benefits (e.g., cost avoidance, freed capacity,

productivity gains) especially in the short term due to the issue of passive reallocation where the redeployment of capacity/resources freed by one particular clinical program area is simply exhausted by other programs which consume that capacity without specific approvals or plans. In order to ensure that providers share in both upside and downside risk, the AHS approach will require programs to track actual performance against the original improvement forecast contained in the business case as a feedback mechanism that will help inform the subsequent budget cycle. Over a longer time horizon, possible real budget adjustments may occur at this step, which would translate capacity gains into actual monetary savings enabling the reallocation of resources to achieve other organizational priorities (clinical and nonclinical).

For ERAS, the case for change was funded by AHS, and the organization has reacted positively with respect to the return (i.e., measured benefits) that it has realized on its investment in ERAS. Moreover, several clinicians have stepped up to drive the change clinically and through their contributions to the international guideline development. With the progress that has been made in guideline implementation, it is now the time to apply shared savings principles, the newest concept of *ERAS for all*, ensuring that all surgical patients across the province are exposed to the guideline fundamentals. Using Gramlich et al.'s work on barriers and facilitators, the business case for change will address issues at the individual, site, and system levels. Using the AHS framework for change proposals (outlined previously), we can now better articulate the benefits that can be expected, understand what clinical and operational changes are required to enable teams to sustain operational and financial performance results, and compare those results to the site-specific deployment plans originally set out in the business case.

Conclusion

In conclusion, the ability to spread and scale ERAS international guidelines is promising, and health systems should consider how to spread and scale this innovation to ensure *ERAS for all*. In doing so, the ability to demonstrate surgical transformation and the value proposition associated with the investment will likely emerge. However, in building the case for change, a robust methodology is recommended to help decision-makers better understand the value that can be created for the health system through the planned deployment of this innovative solution. By clearly articulating and quantifying expected operational and financial results, it will be easier for providers and decision-makers to identify and agree upon strategies for sustaining performance results over the longer term.

Little research has been published about the implementation of multiple guidelines across multiple sites and what levers are being used to maintain or improve outcomes. Studies that examine multiple guideline implementation and return on investment are necessary to better describe the value and the process required to achieve system-wide adoption and change. Furthermore, while some studies outline the value of single-protocol adoption, the impacts beyond the hospital have been poorly studied. Nonetheless, there is promise that ERAS implementation not only produces acute care value but also has an impact on overall health system utilization.

Finally, the role of patients as part of the ERAS team and the ability to better measure and understand their reported outcomes and experience would also add strength to a business case for change. For example, decision-makers require a comprehensive picture of the expected value that will be created should they decide to finance the continued deployment of the ERAS guidelines to all surgical patients in Alberta. This picture can be created by putting together a robust operational and financial forecast of future performance and documenting the case for change and how the health systems will incent performance in order to achieve and sustain planned gains.

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ERAS® Society and Latin America

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Adrian Alvarez and Santiago Mc Loughlin

Introduction

A Global Problem

Weiser et al. estimate that 312 million operations took place in 2012 [1]. This result represents a 33.6% increase over 8 years as compared with a previous report from the same authors [2]. The rate of major complications has been documented to occur in 3–22% of inpatient surgical procedures and the death rate 0.4–0.8%.

Nearly half of the adverse events in these studies were determined to be preventable. Every day millions of people suffer these preventable adverse events, and billions of dollars in costs are generated in the healthcare systems [3]. As expected, low- and middle-income countries (LMICs) have the highest burden of mistreated surgical illness [3].

The Situation in Latin America

Increases in life expectancy have changed previous trends of disease in low- and middle-income countries. With this epidemiological transition, disorders affecting populations are shifting from diseases of pestilence and infection (that are indicators of pre-industrial societies) to those that are identified with industrialized and rising economies. Also, due to technological advances in anesthesia, surgery, and intensive care, the number and complexity of surgeries are steadily growing [4–10]. The complexity of patients is also increasing due to age and comorbidities. The resulting demand is not quantitatively (not all necessary surgeries are performed) nor qualitatively (low compliance to international standards) satisfied. Consequently, perioperative morbidity and mortality are also rising. However, accurate data to understand the real magnitude of the surgical problem in Latin America is, at best, scarce.

Centralized information is often collected inefficiently (or not collected at all) by governmental organizations or large institutions in the emerging countries. The result is the lack of adequate situational diagnosis and an inexistent auditing capacity of the outcomes.

Furthermore, the surgical care of a patient involves different elements of medical treatment occurring in different places at different moments and performed by different professionals. Communication between the healthcare providers involved in the surgical process is rarely enhanced or implemented in a standardized fashion, resulting in a chaotic and non-efficient communicational process. In addition, economic reasons (professionals required to work at more than one hospital or section) and fragmented management structures also contribute to this deficient communication. All these factors acting together result in paralleled, or even opposed, efforts that lead to a disintegrated and extremely variable patient care.

We believe these trends are bound to continue, and perioperative care in Latin America requires a paradigm change. This is the challenge we must face in our region. This will be discussed in this chapter with suggestions for solutions.

The Solution Through the ERAS Approach

As extensively presented earlier in this book, the goal of the ERAS® Society is to develop perioperative care and to improve recovery through research, education, audit, and implementation of evidence-based practices. With this approach, enhanced recovery after surgery (ERAS) programs have accomplished major impact over length of hospital stay and reduction of postoperative complications [11–13].

Although the content of ERAS protocols may vary significantly, a common straightforward logical sequence is repeated for its implementation: plan, do, check, and act. This concept not only takes its origins from business models but also enables a worldwide approach to perioperative care.

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From Assumptions to Facts

Continuous auditing is a basic element of even small business's management that we rarely implement in our medical practice. Control over the processes allows the identification of events at the moment and place they occur, generating the opportunity to reinforce successful interventions or effectively correct mistakes.

Information should not be simply storage but rather be handled in a database management system that interacts with the users, enabling the analysis and projections of different indicators. Inputs should be standardized to allow comparisons (between different periods or institutions) that can contribute to identifying deficiencies and to plan interventions based on real needs and feasibility of potential solutions. Auditing outcomes and processes governing them is a must when it is necessary to plan healthcare policies.

Reliable information and auditing capacity are now within our reach, for example, through the ERAS Interactive Auditing System (EIAS) online platform. In the same way that cell phones have bypassed landlines for providing Internet access in underdeveloped countries, data from the surgical process no longer depends on inefficient centralized institutions. EIAS constitutes an easily accessible and low-cost data management system requiring only Internet access. Internationally standardized data input in this platform enables us to compare our results with the rest of the world in a common language. Moreover, this characteristic may easily enable the first integrated Latin American register of surgical outcomes.

It is important to highlight that, even with the solo effort of a committed professional, adequate data about the quality of care can be obtained and compared to the rest of the world using EIAS.

From Anecdotal Talk to Effective Communication

Although adequate data can be obtained using EIAS, a change in the process of care requires addressing the problem of deficient communication and fragmented care. Individual skills are undoubtedly necessary but, when isolated—when not integrated in a real multidisciplinary, systematic, and coordinated approach—they lead to failures in the process of care. Healthcare providers in our region find a large proportion of their projects dying due to ineffective communication within all professionals involved in the perioperative process.

Effective communication is the key element for the integration of perioperative care. Unlike traditional care, ERAS programs create multidisciplinary teams right from the beginning to facilitate changes where and when required [6]. After a work plan is established, weekly meetings guided by the ERAS® Society team leaders provide the ideal scenario to facilitate effective communication. An effective communication process will then facilitate the teamwork in order to plan, audit, and act according to real facts and not assumptions, as historically happened before ERAS.

From Standardization to Implementation

Standardization's goal is to offer the patients the best possible treatment based on scientific evidence with minimal variability in quality and safety. Despite being an academic hot topic, and its success in other industries, standardization in healthcare has found difficulties in being adopted. Janet Woodcock (director of the US Food and Drug Administration's [FDA] Center for Drug Evaluation and Research) has recently stated that the gap between what research has proven to be good practice and the actual clinical practice of medicine is one of the most critical problems to be faced today [14]. Also, according to Woodcock, the currently separated systems of clinical research and daily practice must converge through the development of a truly learning healthcare system capable of self-evaluation and improvement [14].

Daily practice can be guided by the evidence-based protocols developed by the ERAS® Society with specific content depending on the type of procedure. An interesting aspect of the ERAS guidelines is that evidence may arise from constant data auditing of daily practice and not necessary always from the clinical research setting. These guidelines can be accessed without restrictions through the society's Website and may provide the road map for any team seeking to standardize their surgical care.

The challenge to go from guidelines to a standardized daily care is approached through the ERAS Implementation Programs (EIP) led by certified ERAS trainers. The structure of the training is based on four seminars that are separated by three "periods of action" where the training team performs the tasks indicated on the last seminar. Much of the focus is on introducing highly specific changes to current routines to conform to best practices and using the tools to monitor and analyze the effects of those changes.

The goal of the EIP is to train the unit to change traditional care to evidence-based care. This new paradigm will be characterized by the following features: effective communication within the members of the multidisciplinary team (by weekly or bi-weekly team meetings), consensus about the application of the elements of care (according to ERAS® Society guidelines), and, finally, auditing outcomes and processes involved in the patient care (by using the EIAS) [15–18].

Results from ERAS® LatAm

Before the initiation of the ERAS® LatAm, Professor Aguilar-Nascimento, a surgeon from Cuiaba in Brazil, developed the first multimodal approach in the wards of its Surgical Clinic Hospital ("Hospital Universitário Júlio Muller – HUJM") based on the ERAS Guidelines in LatAm. The program was dedicated to accelerating the recovery of patients undergoing abdominal operations. This project, named ACERTO (www.projetoacerto.com.br), promotes and organizes well-attended annual congresses for the diffusion of the enhanced recovery after surgery principles since around 10 years in Brazil, and Dr. Aguilar-Nascimento and his team have published several important papers highlighting the need for ERAS-related changes in practice, in particular in the field of surgical nutrition in the Brazilian patient population.

The starting point of ERAS® Society Implementation Programs in Latin America was the implementation program led by Robin Kennedy, Olle Ljungqvist, and Jennifer Burch for the "Hospital Italiano de Buenos Aires" in Argentina [12]. This resulted in the first center of excellence of the region that was ready to train units in ERAS according to the ERAS® Society model in 2014. Further than just improving surgical care, team members from this center of excellence were trained to spread the word of ERAS in the region through national symposia, congresses, and other academic meetings. Thanks to these efforts, ERAS programs continue to expand steadily in the region, and several teams followed Argentina in the implementation of ERAS programs. In the year 2015, a team from Colombia ("Clinica Reina Sofia Org Sanitas") and one from Mexico ("Hospital Civil de Guadalajara") started the path of an ERAS Implementation Program. In the following year, two hospitals from Brazil ("Hospital Israelita Albert Einstein" at São Paulo and "Santa Casa de Misericordia de Porto Alegre") started and successfully completed the ERAS Implementation Program. In the same line of work, based on the ERAS guidelines, Dr. Aguilar also from Brazil developed a multimodal approach in the wards of its Surgical Clinic Hospital ("Hospital Universitário Júlio Muller – HUJM") dedicated to accelerating the recovery of patients undergoing abdominal operations. This project, named ACERTO, also promotes and organizes annual seminars for the diffusion of the enhanced recovery after surgery principles. In 2016, two institutions from Uruguay ("Hospital de Carmelo" and "Médica Uruguaya Corporación de Asistencia Médica" de Montevideo) joined our efforts for an enhanced perioperative care in the region. Finally, in the last year, one center from Chile ("Clinica Alemana de Santiago") and the "Sanatorio Guemes" from Argentina also initiated their training in the implementation program (Figs. 62.1 and 62.2).

This strong work has already shown beneficial results similar to the ones reported in Europe and North America. Up to the moment, 1672 patients have been included in our ERAS® LatAm register on the ERAS Interactive Auditing System. Regional median compliance to ERAS guidelines grew from 35% in 2014 up to 66% in 2018 (Fig. 62.3a). During the same period, the average length of hospital stay was reduced from 8 to 6 days (Fig. 62.3b). When analyzed in a multiple regression adjusted by confounding variables (date of surgery, type of procedure and approach, age, American Society of Anesthesiologists [ASA] score, diabetes, and Portsmouth-Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity [P-POSSUM] score), ERAS implementation was associated with a 2.06 days decrease in hospital stay (confidence interval [CI] 95%, −3.27 to −0,86; $p = 0.0007$) as compared to the pre-ERAS patients. Similar results have been observed regarding severe complications and intensive care unit (ICU) stay. More than 3000 days of hospital stay may have been reduced over this period. Hypothetically, the extension of these results to the approximately 25 million people undergoing major surgery in Latin America every year would represent 50 million days of hospital stay spared per year.

However, for this project to reach as many Latin American patients as possible, a strong and committed network is also needed. All ERAS units and all healthcare professionals involved in this change of paradigm of perioperative care in the region should ideally join efforts and work together. Following this line of thoughts, a group of Latin Americans attendees to the 2016 ERAS World Congress agreed to create a chapter of the ERAS® Society in the South America and the Caribbean region. One year later, ERAS® LatAm was founded in Uruguay during the 34th Confederation of Latin American Societies of Anaesthesiology (CLASA). Since then, multiple exchange forums have been organized, and the promotion of ERAS within our region is constantly increasing. ERAS® LatAm constitutes the collaborative network that was needed to provide guidance and support to institutions looking to improve their results on surgical care.

Conclusion

Future Perspectives

Three objectives will guide our collaborative efforts in the near future [19]:

First, to continue with a large-scale expansion of ERAS to as many units as possible through communication (national symposia, congresses, or other academic meetings) and implementation.

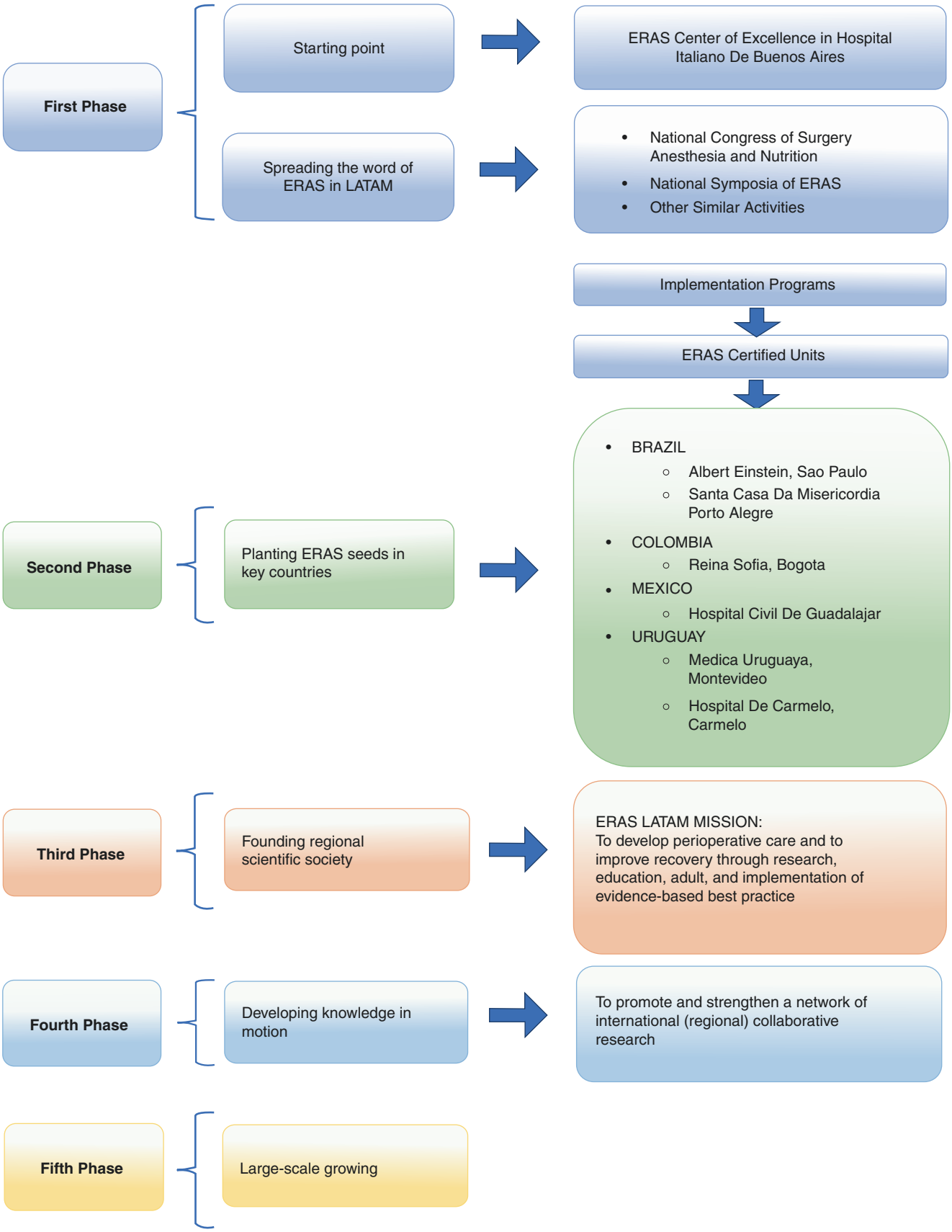

Fig. 62.1 Phases of development of ERAS in the region

Fig. 62.2 Sites and years of ERAS program implementation in Latin America
- 2014: Hospital Italiano de Buenos Aires, Argentina, Center of Excellence
- 2015: Clinica Reina Sofia Org Sanitas, Colombia; Hospital Civil de Guadalajara, Mexico
- 2016: Hospital Israelita Albert Einstein, São Paulo, Brazil; Santa Casa de Misericordia de Porto Alegre, Brazil; Hospital de Carmelo, Uruguay; Médica Uruguaya Corporación de Asistencia Médica, Uruguay
- 2018: Clinica Alemana de Santiago, Chile; Sanatorio Guemes, Argentina.

Fig. 62.3 Impact of ERAS protocols over (**a**) compliance to guidelines and (**b**) the length of stay

Second, to strengthen the networking of all ERAS units mainly by multicentric research. The ERAS approach provides us with a unique opportunity to make this possible. All ERAS-certified units follow similar care pathways (ERAS protocol). Also, all data is collected in the same database, and all our ERAS teams look at our results and audit the processes in the same way (EIAS).

Third, to plan and develop sustainability projects with committed national or regional leaders. Mandatory periodical measurement and diffusion of clinical outcomes in the participating units may be established to correct mistakes or highlight successful efforts. Also, it is vital in this field to continuously promote the participation of all stakeholders and to ensure the empowerment of both patients and healthcare providers.

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ERAS® Society and Asia

63

Kwang Yeong How, Jonathan Jit Ern Tan,
and Manuel Francisco T. Roxas

ERAS and ASIA

Asia is the world's most populous continent in the world and is rapidly developing. Such rapid growth is associated with economic gains but also puts a huge strain on limited resources. Most of the countries in Asia are low- and middle-income countries (LMICs). According to the landmark report of The Lancet Commission on Global Surgery, Global Surgery 2030, access to safe and affordable surgical and anesthesia care is severely neglected in LMIC countries, with South Asia, Southeast Asia, and East Asia accounting for more than half of the unmet surgical needs. One of the recommendations made by the commission to overcome this problem is to scale up surgical and anesthesia services to meet current population needs while maintaining focus on quality, safety, and equity [1].

The emergence of ERAS in Asia is well timed to meet this challenge. ERAS programs are designed to improve outcomes and have been shown to reduce healthcare costs [2]. Although the adoption of ERAS practices in Asia was initially sluggish, momentum has picked up in the last few years with several scattered initatives in different countries including The Peoples Republic of China, Japan and other countries. Not surprisingly, this coincided with the designation of the first two ERAS® Centers of Excellence (CoEs) in Asia: The Medical City (TMC) in the Philippines and Tan Tock Seng Hospital (TTSH) in Singapore in 2016. The objective of this Chapter is to describe the development of the initiatives by the ERAS® Society in Asia (Fig. 63.1).

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Development of ERAS in the Philippines

The Philippines is an archipelagic country in Southeast Asia comprising 7641 islands. It has a population of 110 million, making it the second most populous nation in Southeast Asia. As a middle-income economy, it ranks as the third largest in Southeast Asia [3]. However, the Philippines' healthcare expenditure is at a moderately low 4.5% of gross domestic product (GDP), and out-of-pocket expenditure still accounts for 54.2% of total health expenditure [4. Access to and lack of manpower in healthcare are two of the biggest issues facing the country. Given these challenges, there is certainly a need for quality- and value-based surgical initiatives in the Philippines.

The growth of ERAS in the Philippines began in 2014 with small, uncoordinated steps. First, two former Presidents of the Philippine Society of Colon and Rectal Surgeons (PSCRS), namely, Dr. Manuel Francisco T. Roxas and Dr. Hermogenes Monroy, attended the second World ERAS Congress held in Valencia, Spain. They then started trying to incorporate ERAS into the colorectal programs of two large government hospitals, namely, the Philippine General Hospital and the Jose R. Reyes Memorial Hospital, with only limited success. Fortuitously, Professor Olle Ljungqvist, ERAS® Society President, was invited to deliver a lecture before the Philippine Society of Parenteral and Enteral Nutrition (PhilSPEN) during its annual convention in October of that year. Within that same time frame, and through the efforts of PhilSPEN President Marianna Sioson, Professor Ljungqvist was also able to deliver a lecture on ERAS in TMC, one of the largest tertiary private hospitals in the country, on October 9, 2014. This was a significant event because it enabled Dr. Roxas, director of the Colorectal Surgery Program at TMC at that time, to convince upper management on the value of formally enrolling in the ERAS Implementation Program (EIP).

Hence, 2015 became the landmark year for ERAS development in the Philippines. In May, just before the World Congress of ERAS and Perioperative Medicine held in

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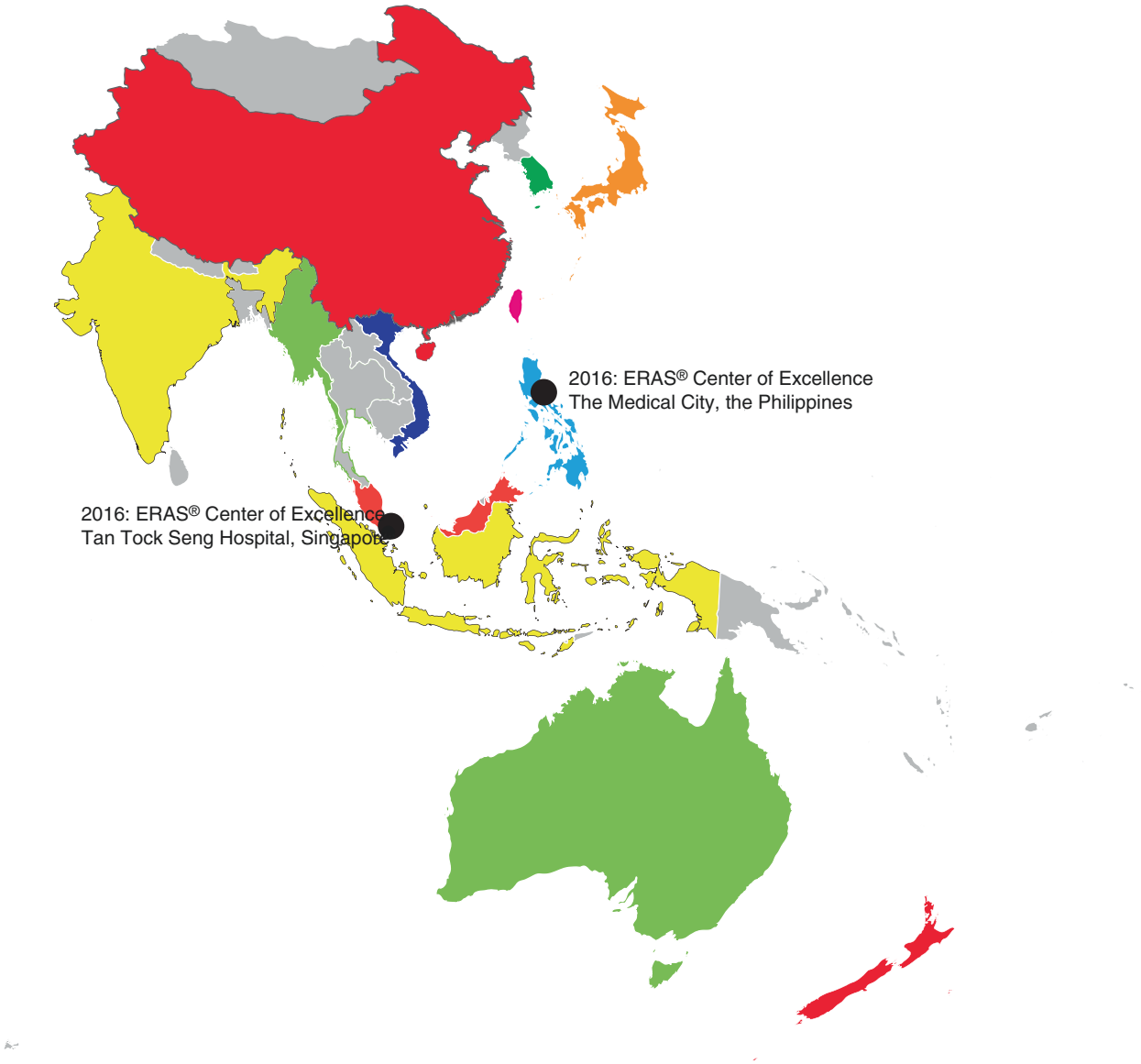

Fig. 63.1 The first two ERAS® Centers of Excellence (CoEs) were established in Asia in 2016: The Medical City (TMC) in the Philippines and Tan Tock Seng Hospital (TTSH) in Singapore (represented as black dots). Interest in ERAS continues to spread across Asia (shown with color on the map)

Washington, D.C., an official contingent from TMC enrolled in the ERAS Implementation Program. Online training and initiation to the ERAS Audit System soon followed. From December 2015 until April 2016, a series of workshops among multinational teams (from the Philippines, Singapore, New Zealand, and South Africa) were held, with Singapore playing host. Local team development and educational activities, as well as team huddles, were also conducted within the hospital. By the end of the EIP, ERAS pathways, patient guidebooks, and patient communication tools had been developed and implemented.

With the implementation of the ERAS program for colorectal surgery in TMC, compliance now hovers at 70% and hospital stay at 4 days, and complications have been significantly reduced. The program won first prize in the 2016 Quality Improvement Awards at TMC and the 2017 Asian Hospital Management Excellence Award. A paper on diabetes and ERAS was presented during the 2018 6th ERAS World Congress in Stockholm. Currently, the TMC program is now being extended to include ERAS in pancreatic, liver, gynecologic, head and neck, and orthopedic surgeries.

These early efforts by the Philippines ERAS Chapter and TMC are the first giant, historic steps toward achieving our common goal of spreading ERAS throughout the Philippines. The Philippine General Hospital is soon poised to be the second ERAS® Center of Excellence in the Philippines, while active recruitment of other hospitals continues.

Development of ERAS in Singapore

Singapore has a population of 5.6 million people and is the third most densely populated country worldwide [5]. Although Singapore is considered one of the most expensive cities to live in, it has consistently maintained low healthcare spending at 2.2% of its GDP [6] while maintaining excellent healthcare outcomes, coming in second in the Bloomberg Healthcare Efficiency Index 2018 [7]. However, similar to what many other countries are experiencing worldwide, healthcare spending is on the rise, and the health ministry is focusing its efforts on improving value in healthcare.

Prior to 2016, the adoption of ERAS practices in Singapore, like in many places worldwide, was fragmented and sluggish. Efforts were mostly based on individual clinicians' preferences and not systematically implemented. Back then, besides TTSH, two other public hospitals—National University Hospital and Khoo Teck Puat Hospital—were known to have included some ERAS components in their colorectal care pathways. However, no formal, consistent audits were done.

In May 2016, TTSH became the first hospital in Singapore to fully implement and integrate ERAS® Society guideline-based protocols and audit—through the ERAS® Interactive Audit System (EIAS)—into its perioperative workflow. In 2013, the hepatobiliary surgical team initiated a Clinical Practice Improvement Program Project that introduced preoperative ERAS elements into the pancreaticoduodenectomy surgery clinical pathway. This project reduced length of stay by 3 days and brought ERAS protocols to the attention of senior management. Following that, in 2015, the colorectal surgery team performed a retrospective internal audit of existing ERAS practices in the colorectal clinical pathway. The audit found that only 16 of the 20 ERAS recommendations for colon surgery were being practiced, and compliance to these practices was only 39%.

In September 2014, Professor Ljungqvist was invited to TTSH by Dr. Doris Ng, then President of the Society of Parenteral and Enteral Nutrition (Singapore) (SingSPEN), to share his expertise and experience in ERAS while he was in Singapore for a European Society for Clinical Nutrition and Metabolism (ESPEN) Life Long Learning (LLL) workshop. The meeting came at an opportune time, as Tan Tock Seng Hospital was evaluating other value-based healthcare systems around the world. ERAS provided an alternative evidence-based model that could provide a method for reducing unwanted variations in clinical practice and ensuring a consistent delivery of optimal outcomes. The discussion soon developed into a real possibility of TTSH joining the ERAS® Society as a trained unit in Asia. This prompted a colorectal surgeon, Dr. Kwang Yeong How, and an anesthetist, Dr. Jonathan Tan, to form an ERAS workgroup consisting of multidisciplinary stakeholders to lead the systematic implementation of ERAS for colorectal surgery in TTSH.

In order to increase awareness and obtain buy-in and acceptance of ERAS practices among the different specialty groups, numerous road shows were conducted by members of the workgroup at all the relevant departments and care areas. It was important that any doubts were addressed before full implementation could take place. Multiple presentations were made to the Hospital Medical Board to garner support and funding to proceed with the EIP. While the hospital's senior management supported the ERAS initiative and saw the value proposition, there was no budget for the EIP nor the EIAS subscription. It was only through the award of a grant from the Ng Teng Fong Healthcare Innovation Programme that the team from TTSH was able to join the EIP in December 2015, along with teams from the Philippines, New Zealand, and South Africa.

In May 2016, the ERAS program in TTSH was officially launched. Together with TMC in the Philippines, TTSH became one of the first two Centers of Excellence in Asia. One year after the full implementation of ERAS protocol in colorectal surgery, the hospital length of stay for colorectal surgery was reduced by a median of 2 days from 7 to 5 days, and readmission rates fell from 11% to 4.6%. A comparison of costs of hospitalization between the pre-ERAS and post-ERAS time periods also showed an average reduction of $1070 per hospital stay [8].

Within TTSH, ERAS protocols were gradually implemented for liver, pancreas, bariatric surgery, gastrectomy, and radical cystectomy by the end of 2017. As more surgical subspecialties became included, there was a palpable shift in attitudes and work practices that could be seen in all parts of the perioperative process. ERAS became a common language among the members of the perioperative team. Surgeons who were previously skeptical started to adopt ERAS recommendations into their practice. Anesthetic practices for the initial ERAS surgeries were being implemented for more and more "non-ERAS" patients as these were recognized as the new standard of care. Spin-off projects that encouraged early mobilization and perioperative nutrition were initiated independently from the ERAS workgroup. Nursing work processes and nursing work redesigns that were driven by ERAS were now being adopted as

new standard work in the wards. This was the paradigm shift in action, a subtle yet undeniable change—a process that some of us coined as the "ERAS Creep."

The hospital leadership also recognized that this was a system that not only consolidated the best evidenced-based perioperative practices but also incorporated a comprehensive method of monitoring outcomes and compliance to process measures that determine those outcomes. The TTSH and regional healthcare senior leadership were convinced that the ERAS methodology and principles can be a good perioperative framework upon which more quality improvement initiatives can be leveraged. This has come in a very timely manner, as the healthcare system in Singapore was undergoing a major shift in its policies, with an increasing focus on value-driven outcomes.

The efforts put in by the team and the good results did not go unrecognized. In 2016, the team won gold and bronze awards at the Singapore Health and Biomedical Congress. In 2017, the ERAS team was awarded the silver award during the National Healthcare Group Team Recognition Award Ceremony.

TTSH is also determined to contribute and play an active role at the international level. In 2017, at the 5th ERAS World Congress in Lyon, TTSH presented four posters. This increased to ten posters and two oral presentations at the 6th ERAS World Congress in Stockholm in 2018.

Lessons Learned from the Singapore Journey

Redesigning "Established" Workflow

Through the EIP, our team identified weaknesses, deficiencies in the old perioperative process, and put in place a revised and improved workflow. The ERAS protocols and compliance points were used to set up new micro processes that would enable the patient's journey through the ERAS process with the highest compliance. One of the lessons learned during the EIP was that many things perceived to be functioning optimally and taken for granted previously were actually far from ideal. For example, the allocation of timeslots at preoperative assessment clinics to accommodate separate anesthetist, dietician, and physiotherapist assessments in a single visit, or the logistics of making oral nutritional supplements easily available for patients in the wards, all involved a significant amount of planning, problem-solving, and thinking out of the box, as well as work redesign.

Resources provided by ERAS® Society and Encare, including ERAS patient education material and patient diaries, were adapted to the Singapore context and put into practice. This was most apparent in the language situation in Singapore. Even though English is the primary language used for communication, many of the elderly Singaporeans still speak and understand their native languages of Chinese, Malay, Tamil, and other dialects. This meant that we had to have the ERAS patient guidebook in English and also translated into Chinese, Malay, and Tamil.

The "Deconstructed" ERAS Nurse

Another major challenge we faced was the difficulty in having a dedicated ERAS nurse, a role that seemed to be crucial to the success of the ERAS program. The nursing leadership of our hospital was moving away from training more specialty nurses; thus the request for a dedicated ERAS nurse was declined. There were also no funds to employ any extra nurses. To circumvent this problem, the role of the ERAS nurse was therefore dissected into the preoperative, intraoperative, and postoperative roles, and a "deconstructed" ERAS nurse model was born. In order for this model to work, besides knowing and performing their own roles very well, nursing leads in each of these perioperative phases also need to have a comprehensive understanding of what their counterparts do in the rest of the ERAS patient journey. Communication between the nursing leads is also of vital importance for the process to be smooth. Here, ERAS compliance sheets are used to facilitate handovers between nurses. A hospital-level ERAS nursing committee was also set up to facilitate implementation of ERAS practices throughout all care areas, wards, and nursing services.

This model of care was a major change in the way ERAS was implemented effectively in the published literature. An unintended benefit of this model was that more nurses were trained to understand and perform the role of the ERAS nurse throughout the perioperative workflow. In the long run, there is less reliance on a single individual, making this a more sustainable model for ERAS nursing, as nursing staff turnover is traditionally high. This "deconstructed" nursing model with multiple linkages is perhaps a model of care that other resource-limited units, especially in Asia, may adopt successfully.

Sustaining ERAS in Tan Tock Seng Hospital

One of the common problems that ERAS units face is the sustainability of the program after successful implementation. In TTSH, we observed that even as the ERAS program continues to mature and ERAS processes become part of standard daily workflow, expansion to other subspecialties meant that more practitioners became involved and processes became more complex. Issues with consistency and compliance started to surface.

To deal with these problems, our team continues to meet fortnightly to review results, make improvements, and set directions for the program. Stakeholders from other subspecialties teams are actively engaged and refresher EIPs are conducted for them. Making use of technology, ERAS compliance and audit measures have been incorporated into the TTSH electronic medical records so that data audit becomes more reliable and consistent. An ERAS-centered perioperative mobile app is also being developed to help the team individualize the patient's perioperative journey, incorporating

pop-up reminders, gamification to encourage and motivate early postoperative mobilization with the use of step trackers, and food diaries to record calorie intake.

Scaling ERAS in Tan Tock Seng Hospital

While other surgical subspecialties have started to adopt ERAS protocols, the challenge has been to replicate the same enthusiasm, commitment, and passion to adhere to and audit the true ERAS elements. Moving forward, the ability to scale ERAS to other subspecialties in TTSH needs to take on a different approach from the initial ground up model of the pioneering colorectal ERAS team. Hospital leadership has made ERAS implementation and spread a top priority and now needs to help drive that vision and provide help and resources in the form of protected time, finances and manpower, so that teams on the ground face less obstacles and resistance in implementing ERAS in their subspecialty practices. The core ERAS workgroup needs to continue to support the other teams by providing repeated training and setting up the infrastructure for all subspecialties; facilitating discussions and conversations between the hospital administrators and other subspecialty teams; reviewing outcomes and results regularly with all the teams; and using the EIAS data to encourage improved compliance.

Spreading ERAS in the Region by Tan Tock Seng Hospital and the Medical City

In the Philippines, the principles and practice of ERAS have not permeated into the mainstream of surgery practice; thus, its benefits have yet to reach a majority of Filipino patients. In Singapore, most public hospitals are incorporating some practices of ERAS to perioperative care. However, it is unclear what the outcomes and compliance levels are in these programs, as each hospital monitors outcomes separately and has different approaches to implementation. It is also not known the extent to which ERAS protocols have been implemented in each hospital. This also means that it is difficult for the hospitals to combine their data and results to make meaningful interpretations at a national level.

In September 2016, TTSH, TMC, and the ERAS® Society organized the first National ERAS Symposiums of Singapore and Philippines. This collaboration and sharing of resources has continued with the second and third National ERAS Symposiums in 2017 and 2018 (Fig. 63.2). As ERAS® Society President, Professor Ljungqvist has been a constant fixture in all three symposiums in both countries. Other speakers include Professors Anders Thorell, Dileep Lobo, Michael Scott, and Bernhard Riedel.

Interest in ERAS on national levels has increased significantly since the first National ERAS Symposiums in 2016. As national ERAS Centers of Excellence, TTSH and TMC have actively engaged the ERAS teams of different local hospitals and facilitated discussions with the ERAS® Society. The Philippines ERAS Chapter was officially launched on August 28, 2015, and the Singapore ERAS Chapter was inaugurated at the third Singapore ERAS Symposium on September 22, 2018, to increase inter-hospital and institutional collaborations. The aim is to have more hospitals in Singapore and the Philippines join the ERAS® Society network and be on the same platform for implementation and audit of results.

Fig. 63.2 The 2nd Singapore ERAS Symposium in 2017

On a regional level, both Asian ERAS® CoEs have been actively promoting the ERAS philosophy and practice in the region. The team members have been invited to various countries in Asia, including Malaysia, Indonesia, Thailand, Vietnam, Taiwan, and China to share their experiences on the implementation of ERAS. TTSH also hosted several groups of doctors from Indonesia, Thailand, Vietnam, Hong Kong, and Taiwan to experiential workshops of the ERAS patient journey between 2016 and 2018. These included introductory lectures and real patient encounters in the preoperative clinics, operating theaters and postoperative wards, as well as small group discussions. One of these groups was from Vinmec Times City Hospital, which subsequently underwent an EIP conducted by the TTSH Team in March 2018—the first to be conducted by an Asian CoE.

Future of ERAS in Asia

Current Status and Challenges of ERAS Implementation in Asia

ERAS development in Asia is still very much a work in progress. There is a huge variation in the awareness and practice of ERAS across Asia. Some hospitals in major developed cities are already applying ERAS practices well, while at the other extreme, there are places where the knowledge is still

significantly lacking. Lack of outcome audit and compliance data of any sort is common.

Many of the LMIC countries in Asia do not have basic standards of care, which developed healthcare systems take for granted. Nutrition optimization perioperatively is a luxury where malnutrition may be common in the community and scientific oral nutritional feeds are simply not available. Basic patient physiological monitors and anesthetic and surgical instruments limit implementation of current standards of care. It is precisely in these areas of need that the patients will benefit from a systematic, evidenced-based, protocol-guided enhanced recovery perioperative program.

As a start, ERAS® Society guidelines can form the backbone from which clinical improvement projects may be implemented to introduce some ERAS practices—perhaps starting with what is most easily implementable with the biggest outcome effects. These "ERAS" program efforts must then be audited with a modified ERAS audit system where the positive results can then be used to drive the healthcare system to implement more ERAS elements, with the ultimate aim of implementing and auditing all the elements on the same yardstick as all other ERAS centers around the world. Collection of standardized outcome and process measure indicators will allow countries to monitor progress over time, as well as benchmark their performance against that of other countries at similar levels of development. The EIAS may be a truly cost-effective solution to help developing countries focus on improving surgical outcomes by tracking process measures while enabling benchmarking across the world on common definitions.

Roles of ERAS® Society and Centers of Excellence in Asia

TTSH in Singapore and TMC in Manila are currently the only two Centers of Excellence in Asia. Vinmec Times City Hospital, part of a private group of hospitals in Vietnam, is only the third ERAS unit in Asia to undergo an EIP, which was due to be completed in early 2019.

Challenges and limitations will vary between countries and may be unique within Asia. The ERAS® Society can play a pivotal role in improving perioperative care standards in this part of the world by introducing and standardizing ERAS practices here.

TTSH and TMC, as Centers of Excellence in Asia, are the most well positioned to help our neighbors overcome similar obstacles. Building up the Asian ERAS network of hospitals and linking up with the ERAS world community will help centers in Asia and LMICs build successful ERAS programs for better patient outcomes.

As part of our ongoing efforts to promote ERAS in Asia, the ERAS® Society, TTSH, and TMC collaborated to hold the 1st Asian ERAS Congress in 2019. The establishment of Asia ERAS Congress serves to bring the best of the ERAS World Congress, adding focus to what is most relevant in Asia, and make the congress more accessible to our region. This is a small but significant step toward establishing a wider network of ERAS-trained units in Asia. The vision is that Asia ERAS will be an annual or biennial event, hosted by an Asian ERAS Chapter consisting of leading ERAS centers from all over Asia and supported by the ERAS® Society.

At the time of writing, it is encouraging that discussions are taking place between the ERAS® Society, the two Asian CoEs, and several hospitals in Singapore, the Philippines, Malaysia, Taiwan, Hong Kong, Thailand, and South Korea on training these hospitals to become lead hospitals in their countries.

Conclusion

Besides continued efforts by the ERAS® Society to reach out within Asia, the impetus for change also has to come from clinicians on the ground, as well as administrators and policy makers. International healthcare agencies, charitable organizations, and industry partners can also play a bigger role in supporting the EIPs for hospitals, where resources may be obstacles to implementation. This multipronged approach would set up a conducive climate for a multilaterally beneficial collaboration for all parties.

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ERAS for Low- and Middle-Income Countries

64

Ravi Oodit and Kelly McQueen

Introduction

Since the early 1990s, there has been a significant shift in disease burden in low- and middle-income countries (LMICs) [1]. For the preceding decades, communicable diseases predominately influenced premature disability and death in LMICs. The availability of universal treatment for human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS), and prevention and improved treatments of other infectious diseases, allowed for increased longevity and a shift in disease burden toward noncommunicable diseases (NCDs.) Noncommunicable diseases, including cardiovascular disease, cancer, and trauma, have since eclipsed communicable diseases in LMICs as contributors to premature disability and death (Fig. 64.1) [2]. This epidemiological shift has elevated the need for surgery and safe anesthesia in LMICs, since many NCDs require surgical care for diagnosis, treatment, or palliation. Unfortunately, surgical care and anesthesia has been neglected in LMICs for decades [3].

The prevalence of communicable disease in LMICs prior to 1991 demanded that a majority of healthcare infrastructure and resources in LMICs be focused on preventing and treating these disease states. During this time frame, many global health specialists—physicians, healthcare systems, and Ministries of Health in LMICs—believed that only emergency surgery was a worthwhile investment and that basic surgery was a luxury [4]. Therefore, little investment in surgical infrastructure occurred in LMICs during this time frame, leaving most LMICs with few trained surgeons, even fewer trained anesthesia providers, and limited operating theater space and equipment. These realities meant that few patients had access to surgery in LMICs [5], and for those who avoided or survived communicable disease, there was a huge increase in the prevalence of surgical disease and in the resulting premature disability and death. The expanding burden of surgical disease went largely unnoticed by the global health community until 2015 when three pivotal events occurred. The 3rd Edition of The *Disease Control Priorities in Developing Countries* volume on Essential Surgery [6], the Lancet Commission on Global Surgery [7], and the World Health Assembly Resolution on Safe Surgery and Anaesthesia as part of Universal Health Coverage [8] were published in series in mid-2015, shifting the perception of surgery and anesthesia from a "luxury" to "essential." Since May 2015, many efforts are underway to improve and scale up surgery and safe anesthesia in LMICs.

Many middle-income countries, and most low-income countries, have had to evaluate their surgical systems and invest not only in surgical and anesthesia infrastructure but also the training of additional surgeons, anesthesiologists, and other anesthesia providers. For many countries, these processes are only beginning and will take decades to scale up to providing essential surgery for all in need. The Lancet Commission on Global Surgery estimates that 5 billion humans are in need of essential surgery and safe anesthesia and that more than 143 million surgeries will be needed annually to meet the global burden of surgical disease [7]. The process facing most LMICs is daunting at best and is being facilitated by the National Surgical, Obstetric, and Anesthesia Plans (NSOAP) process [9]. Zambia, Ethiopia, Tanzania, and Rwanda have undertaken this process and are providing examples regionally and across the globe for other LMICs.

Most of the surgical systems in LMICs continue to provide emergency and some basic surgery as the scale up toward the universal provision of basic surgery (Table 64.1) progresses. Currently the surgical care provided however is often poorly executed, anesthesia care is limited, and both result in high complication and mortality rates [10, 11].

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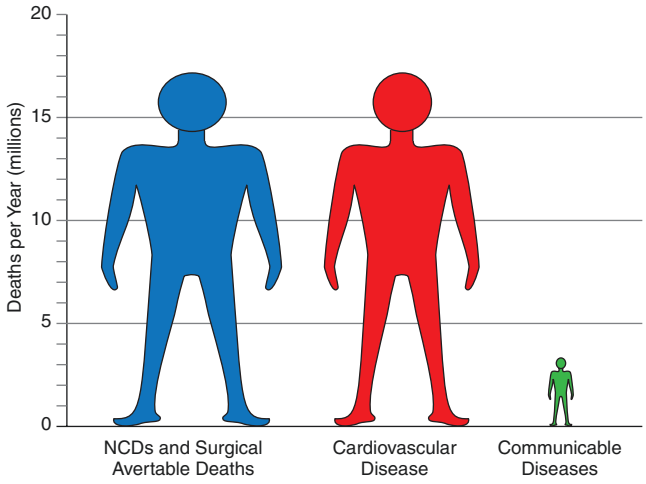

Fig. 64.1 Deaths for communicable disease, cardiovascular disease, and surgical disease

The simultaneous scale up of surgery and safe anesthesia in low-volume countries [12] across the globe (Fig. 64.2) [5] offers a unique opportunity for standardization and protocolized care that may save healthcare dollars and improve complication and perioperative mortality rates. Enhanced recovery after surgery (ERAS) programs have provided a system that focuses on standardized care, with an evidence-based approach to preoperative, intraoperative, and postoperative care, including pain management.

Implementing evidence-based guidelines, standardizing perioperative care, developing well- functioning teams, monitoring and measuring patient outcomes, and recovery and measuring compliance to guidelines are likely to reduce complications, length of hospital stay (LOS), and costs. The access to quality data will assist in benchmarking, monitoring, and continuous improvement. The ERAS care pathway provides an ideal platform to achieve this goal.

ERAS in Low- and Middle-Income Countries: Barriers, Challenges, and Opportunities

Embracing standardization and implementing ERAS in LMICs will require significant modification of protocols used in high-income countries (HICs) and careful consideration of the very limited resources for surgery and anesthesia in most LMICs. Designing ERAS for LMICs, and implementing appropriate guidelines, will need to take into account the limited access to healthcare; delays in seeking, reaching, and receiving care; the resource-constrained health systems; the nutritional status of the population; the high

Table 64.1 The 44 basic procedures recommended for all hospitals in LMICs

Dental
Extraction
Drainage of dental abscess
Treatment for caries
Obstetric, gynecological, and family planning
Normal delivery
Cesarean birth
Vacuum extraction or forceps delivery
Ectopic pregnancy
Manual vacuum aspiration and dilation and curettage
Tubal ligation
Vasectomy
Hysterectomy for uterine rupture or intractable postpartum hemorrhage
Visual inspection with acetic acid and cryotherapy for precancerous cervical lesions
Repair obstetric fistula
General surgical
Drainage of superficial abscess
Male circumcision
Repair of perforations (perforated peptic ulcer, typhoid ileal perforation, etc.)
Appendectomy
Bowel obstruction
Colostomy
Gallbladder disease (including emergency surgery for acute cholecystitis)
Hernia (including incarceration)
Hydrocelectomy
Relief of urinary obstruction; catheterization or suprapubic cystostomy (tube into the bladder through the skin)
Injury
Resuscitation with basic life support measures
Suturing laceration
Management of non-displaced fractures
Resuscitation with advanced life support measures, including surgical airway
Tube thoracostomy (chest drain)
Trauma laparotomy
Fracture reduction
Irrigation and debridement of open fractures
Placement of external fixator; use of traction
Escharotomy or fasciotomy (cutting of constricting tissue to relieve pressure from swelling)
Trauma-related amputations
Skin grafting
Burr hole
Congenital
Cleft lip and palate repair
Club foot repair
Shunt for hydrocephalus
Repair of anorectal malformations and Hirschsprung's disease
Visual impairment
Cataract extraction and insertion of intraocular lens
Eyelid surgery for trachoma
Non-trauma orthopedic
Drainage of septic arthritis
Debridement of osteomyelitis

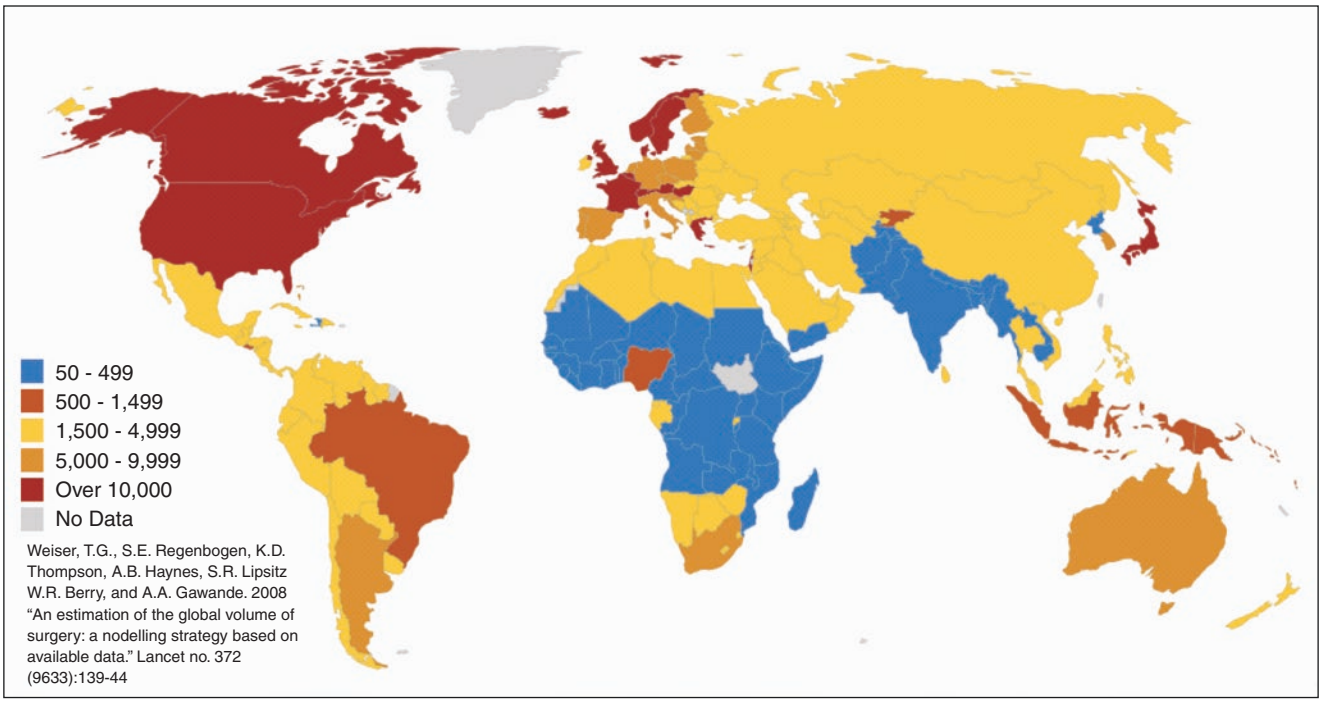

Fig. 64.2 Worldwide surgical volumes. (Reprinted with permission from Weiser et al. [5])

prevalence of HIV; the burden of disease; and the economic status of the country. In addition, guidelines will need to be constructed to include cost-effective and readily available medicines and supplements.

Access to Healthcare

The Global Surgery 2030 agenda [7], and the *Essential Surgery: Disease Control Priorities, third edition* (DCP3) recommendations [1] have opened the door for improving access to basic surgery and safe anesthesia, and the World Health Assembly (WHA) Resolution # 68.15 [8] and NSOAPS [9] have catalyzed scale up to address the large unmet surgical needs in LMICs.

Sustainable change can only be achieved by health systems that are supported by Ministries of Health to include resources for surgical care and safe anesthesia. The access required includes the 44 basic surgeries recommended by DCP3 (Table 64.1) [1], along with additional emergency surgery and the resources to support complete care of the surgical patient, including critical care services within the highest level of hospital care. To achieve not only access, but also good outcomes, the healthcare systems scaling up to surgical care should focus on standardized, evidence-based care that is cost-effective and supported by quality data. For many LMICs, this will include a new focus on preoperative care and patient preparation before surgery.

Preoperative Evaluation and Optimization

Currently there is limited or no availability of dedicated preoperative clinics in LMICs, and most patients are seen the day before surgery by the managing team. In many surgical settings in LMICs, there is also limited laboratory and medical evaluation capacity, including for echocardiograms and advanced imaging such as computed tomography (CT) scans and magnetic resonance imaging (MRI). Therefore, currently there is limited preoperative preparation and a limited ability to optimize patients. It is unlikely in the current surgical environment in LMICs that patients would be delayed for further testing, which may not be available anyway. In addition, many surgeons in LMICs will not focus on patient optimization, in spite of the benefits and cost reductions that are proven and ubiquitously understood in HICs. During planning for NSOAPs and the scale up of surgical care in LMICs, the addition of preoperative evaluation and testing should be considered.

Discharge Planning

Early discharge of postoperative patients might not be as easily achieved in LMICs as in high-income countries. In LMICs patients have limited access to transport and healthcare facilities. Patients who develop postoperative complications at home are likely to return late. Hence surgeons

might be hesitant to discharge patients earlier. The benefits of early discharge to both the patient and the healthcare system may not be realized, and patient care could be compromised if discharge occurs without adequate support systems in place.

Prior to solutions for perioperative management—including preoperative evaluation and optimization and discharge planning being reached—ERAS goals and processes will need to be modified for LMIC settings. Areas of importance and early consideration in the planning process for ERAS in LMICs include standardization of perioperative optimization goals, perioperative discharge planning, and realistic follow-up plans for patients who live long distances from the operative facility. Surgical conditions that currently have long waiting lists for surgical intervention may offer a window of opportunity to optimize patients, but will require restructuring of current practices. Similarly, in the postoperative period, creative solutions for follow-up should be considered. Possible solutions include follow-up clinics in remote areas, phone follow-up (when patient families have phones), alarm symptom checklists, and after-hours call options. Clear preoperative discharge planning to identify and address any barriers to discharge is essential. When family phones are available, a single on-call telephone number that gives patients and their families immediate access to the managing team is helpful, as are daily calls to the patient following discharge. In addition, the use of mobile health platforms, and home visits by community healthcare workers, may assist in discharge and follow-up success. However, locally developed and relevant solutions will need to be considered, since much of what is proposed here may not yet exist in most LMICs.

Cost Implications

The most important cost amelioration opportunity for LMICs is that potential health system and patient savings are possible when standardized approaches are utilized and length of hospital stay is shortened. Significant resources are required to implement and maintain the ERAS program. Costs include salaries for the ERAS nurse coordinator, data capturer, administrator, the implementation program, database management, education, research and training, regular team meetings, nutritional support, and computer hardware and software. LMICs face the additional challenges of inadequate infrastructure that includes equipment, drugs, pathology, radiology, managerial support, transport, ambulance service, safe water, electricity, and adequate and reliable Internet connection.

Innovative solutions will be needed. All stakeholders should be engaged as there is significant potential for mutual benefit. Seed funding could be an option to implement the program. Partnerships with governments and private companies could provide seed funding.

The data from HIC show that once ERAS is implemented, a cost saving of 10–20% can be achieved. Local cost-benefit analysis will need to be conducted in LMICs to guide the implementation of ERAS. If similar savings can be achieved, it could be used to offset the start-up costs and expand the program.

Nutrition

Malnutrition and obesity are significant public health problems in LMICs; 62% of the world's obese population reside in LMICs. This has occurred alongside a large burden of underweight populations in many LMICs.

Obesity adds to the complexity of surgery and perioperative care. It is also associated with increased comorbidities, higher complication rates, and longer length of stay. Malnourished patients have significantly higher morbidity and mortality, a longer length of stay, and increased hospital costs [13–15]. Improving the patient's nutritional status prior to surgery is associated with improved outcomes.

The benefits of the ERAS program may not be fully realized if patients are not nutritionally assessed and optimized preoperatively. This could be difficult to achieve in LMICs, where resources are limited, nutritional optimization is not prioritized, and funding for supplements is difficult to source.

Routine nutritional assessment and support, a key element of the ERAS program, is not traditional practice in LMICs. To address this, dieticians will need to play a larger role in assessing, monitoring, and supporting patients. The current shortage of dieticians in the LMICs will need to be addressed [16]. In addition, all ERAS team members will need training and education on the importance of preoperative nutritional assessment and optimization. Funding will also be required for appropriate nutritional support, monitoring, and measurement.

Human Immunodeficiency Virus

Because the brunt of the HIV epidemic globally is borne by LMICs, the impact of HIV/AIDS must be considered throughout the perioperative period. Perioperative HIV status testing is neither routine in HICs nor in LMICS; therefore the signs of HIV infection—including weight loss, micronutrient deficiencies, malabsorption, and altered immunity and metabolism—must be considered for every patient in LMICs. There is conflicting and limited evidence of the impact of HIV status on postoperative patient outcomes following surgery, but this must be considered as scale up to surgical care is planned [17, 18].

Proposed First Steps for Low- and Middle-Income Countries

In spite of the many challenges and barriers to considering ERAS for LMICs, there are many benefits to even highly modified ERAS processes that may benefit surgical patients and systems in resource-constrained systems [19]. Included in early implementation of ERAS principles are cost-savings related to standardized approaches to patient care, fewer complications, and a reduction in hospital stays. Equally important is the potential for decreasing life-threatening complications including deep vein thrombosis and perhaps decreasing intraoperative and perioperative death rates.

A discussion on ERAS must begin at a very basic level in LMICs, including all stakeholders: Ministries of Health, hospital systems, physicians, and nurses. This scope of buy-in is essential because most of what is required for a successful ERAS program may not yet exist in the most resource-constrained systems. To get started, key stakeholders must acknowledge that standardization will benefit the scale up to surgery and safe anesthesia, and all must agree on the basic elements of surgical care that ERAS has been proven to impact. We proposed that the ERAS framework be applied to all basic and emergency surgery in LMICs, rather than be limited to the specialty surgery for which ERAS was designed in HICs. We also propose that these considerations should be grouped as perioperative, intraoperative, and postoperative. As well, we hope that LMIC readers will appreciate that our initial recommendations are the basic building blocks of modern surgical care and that, ideally, as resources allow and surgical volume increases, ERAS processes will evolve to look more like ERAS systems in HICs, for the greatest benefit to patients.

Preoperative Considerations

As mentioned previously, in many LIMCs preoperative evaluation is limited or not available. Evaluation, patient selection, and patient optimization, however, are essential to the surgical scale and honestly to surgical programs worldwide. Where little or no preoperative evaluation before the day of surgery exists, this must be step one. Resources must be allocated for preoperative screening, and considerations must be agreed upon for patient optimization and scheduling. For these goals to be reached, human resources, laboratory support, and other testing must be available. While a dedicated space, a preoperative clinic, is optimal, creative solutions such as visiting preoperative nurses or a mobile clinic may prove useful. The basic components of preoperative care are outlined in Fig. 64.3. Laboratory testing and basic testing to include electrocardiogram (ECG) evaluation may not be universally available, but is an important step forward in preoperative evaluation.

Intraoperative Management

As LMICs scale up to provide basic surgery in most hospitals, the standardization and modernization of surgical care and anesthesia are important. The ERAS approach has benefit for every surgery in LMICs, since the basic tenets of ERAS focus on physiologic normalcy. This approach includes a modern nil per os (NPO) approach before surgery: clear liquids up to 2 hours before surgery and in some cases providing a carbohydrate drink in advance of surgery. Intraoperative planning for the least invasive approach to any surgical procedure is optimal, and closing the surgical wound without drains whenever possible has been shown to decrease complications. From an anesthesia perspective, providing a standard anesthetic with multimodal pain management and keeping the patient normovolemic is ideal. Preventing hypothermia and controlling blood pressure, while avoiding long periods of hypotension, is also a goal for all surgery (Fig. 64.4).

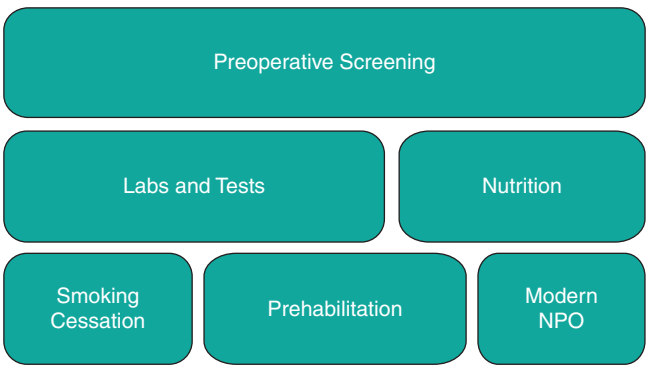

Fig. 64.3 Preoperative evaluation

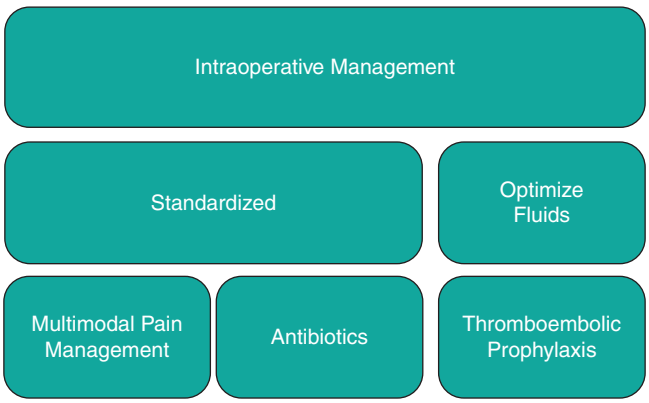

Fig. 64.4 Intraoperative management

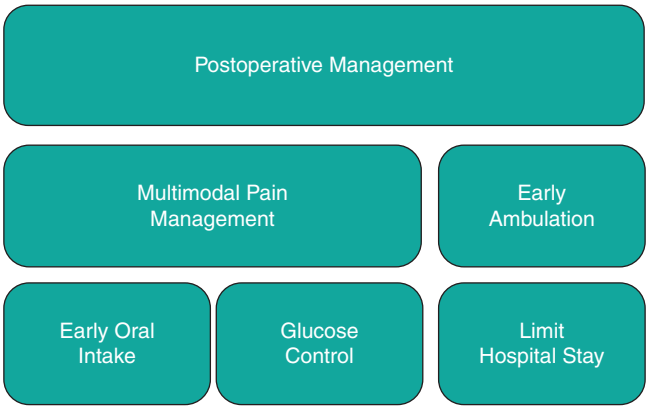

Fig. 64.5 Postoperative management

Postoperative Management

Similar to the basic preoperative and intraoperative management goals described previously, the postoperative management approach focuses on a standardized, evidence-based approach that will improve outcomes and decrease costs in LMICs. The basic postoperative approach for all surgical interventions includes multimodal pain management, early ambulation and oral intake, glucose control, and early planning for discharge (Fig. 64.5).

Data Collection and Management

The role of data within the ERAS protocols is essential. But in many middle-income countries and most low-income countries, the collection of data and the management to follow is a tremendous challenge. Firstly, electronic medical records are often unavailable, and computer systems are not routinely used within the hospital systems. Secondly, and of equal importance, is the workforce. In most LMICs the surgical workforce is significantly understaffed. This is well-documented within the Lancet Commission [7] and is a focus for scaling up the basic surgery in all hospitals. The existing workforce—nurses and physicians, as well as medical assistants and clinical officers—are consumed with caring for patients. With this in mind, data collection for ERAS in these settings will also require modification and, in many cases, simplification.

Surgical indicators, such as infection rates [20, 21] and perioperative mortality rates [22, 23], may offer initial and easy-to-collect benchmarks for the impact of ERAS.

Monitoring and Evaluation

Currently, most LMICs that are engaged in scaling up to basic surgical services and safe anesthesia will find it difficult to manage additional tasks, including monitoring outcomes and evaluating the proposed standardized approaches. In LMICs with limited access to computers, the Internet, and personnel, capturing and entering data may prove a significant challenge. Finding solutions to this prior to implementation will ensure downstream benefit for the ERAS program.

The ERAS(R) Interactive Audit System for monitoring and evaluation system is an integral part of the implementation program, as it allows the teams to continuously monitor their compliance to the guidelines, measure their outcomes, and effect change.

ERAS Guidelines in Low- and Middle-Income Countries

Many of the recommendations for a universal ERAS approach in LMICs will require a paradigm shift in patient preparation, intraoperative management, and discharge planning in LMICs. For this reason, and to assist in utilizing ERAS during scale up to greater access to surgery and safe anesthesia, we highly recommend the creation of guidelines for ERAS in LMICs to assist in the process. The creation of such guidelines will require input from surgical and anesthesia providers working in LMICs and from the local hospital systems and Ministries of Health. Once these guidelines are drafted, it is highly desirable that the recommended processes be tested in situ and then eventually included in NSOAP planning.

An initial evaluation of ERAS interest and the resources required to begin ERAS processes is highly recommended and could be considered in concert with an NSOAP evaluation. Figure 64.6 demonstrates the proposed steps for such an evaluation in LMICs.

Conclusion

Enhanced recovery after surgery has improved surgical care and outcomes and decreased costs in HICs. These benefits are greatly needed as scale up to universal access to surgical care and safe anesthesia continues in LMICs. Existing ERAS protocols offer much needed standardization and structure to systems scaling up for the provision of basic surgery, but must be modified for the realities of healthcare in LMICs. Implementation of the ERAS Care System in LMICs could provide a platform to facilitate implementation of the Global Surgery 2030 goals, improve patient outcomes and service efficiency, and reduce hospital bed days.

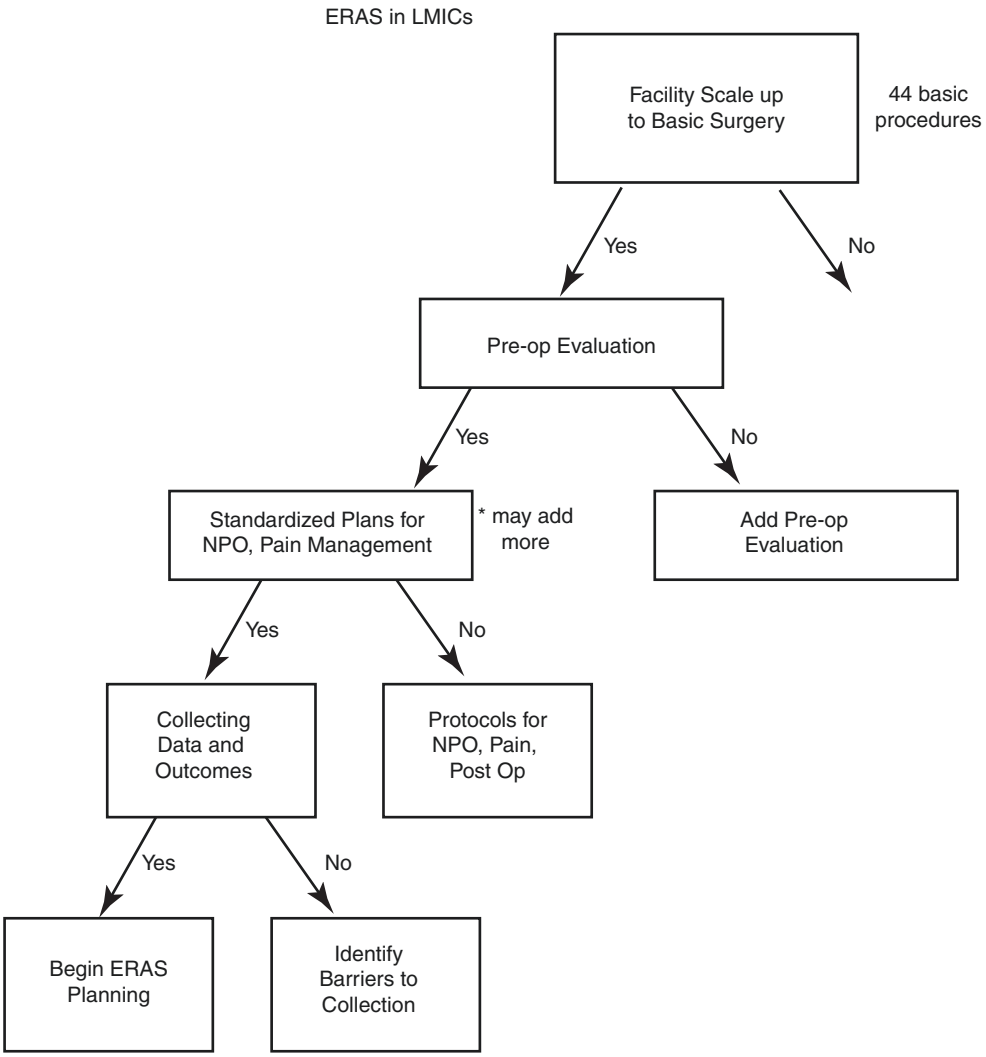

Fig. 64.6 Initial evaluation for ERAS planning in LMICs

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ERAS Position in the Global Surgical Community

65

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Introduction

The concept of enhanced recovery after surgery (ERAS) has been mooted since the 1990s. This chapter discusses the initial stages of ERAS, growing as a concept from a group of academic Northern European surgeons, forming as the ERAS® Society, to its current status in continental Europe. The successes of national implementation in the United Kingdom are covered, as well as efforts in Canada and Australasia. The implications on cost dynamics and opioid use, both of which are topical issues in the United States, are discussed in brief. This chapter provides an overall summary of the burgeoning efforts of health authorities to establish ERAS outside of Europe and North America. The current collaborative efforts of the global surgical community are highlighted, alongside the future applications of ERAS to benefit patients and improve healthcare system efficiency and efficacy within the World Health Organization's (WHO) Global Surgery 2030 vision.

Enhanced Recovery After Surgery: Position in the Global Surgical Community

As previously discussed in this book, ERAS is the acronym for enhanced recovery after surgery, which describes a multimodal approach to optimizing perioperative care in surgical patients utilizing evidence-based methods. The first model of ERAS was developed in the 1990s in Denmark by Professor Henrik Kehlet and was called "fast-track surgery" [1]. The fast-track surgery protocol was applied in a landmark series of colectomies and demonstrated improvements from the conventional 9 to 10 days length of hospital stay (LOS) following the operation to discharging patients within 2–3 days with improved functional outcomes [2]. "Enhanced recovery programs (ERP)" and "fast-track surgery" are terms used frequently to describe these perioperative programs, which have become increasingly common in the global surgical community for demonstrated health benefits for patients, as well as for cost-effectiveness for healthcare providers. The term "fast-track surgery" has since been superseded for its implied perception of focusing on just expedited discharge from surgery [3]. ERAS promotes the recovery pathway of patients as a whole and focuses on adapting protocols to this recovery, rather than solely targeting for faster discharges.

The development of the concept of ERAS as a multidisciplinary and multimodal perioperative approach using evidence-based medicine was first established by a group of academic leaders in a meeting in London in 2001. There were concerns that despite increasing evidence on best perioperative care for patients, these were either practiced in a piecemeal fashion or not yet adopted into standard practice. The decision to establish a set of perioperative protocols and an audit process to continuously measure outcomes into a program to be implemented culminated in the establishment of the nonprofit ERAS® Society in 2010.

The ERAS® Society is the end result of the ERAS Study Group, a group of academic clinicians concerned with improving outcomes using best practices who agreed to establish an international network to discuss the newest research and guide implementation of the resulting protocols. True to the international nature of ERAS, the Study Group itself was formed following a meeting in a London nutritional symposium by the initial founders Professors Ken Fearon (United Kingdom) and Olle Ljungqvist (Sweden). With a slogan of Improving Perioperative Care Worldwide, the ERAS® Society serves an important role as a movement in the dissemination of protocols and evidence-based approaches to care in a global surgical setting.

Since 2005, a series of ERAS® Society consensus guidelines have been published in different surgical fields. The individual chapters of the ERAS® Society in each member

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country ensure a uniform approach to the spread of evidence-based perioperative care. Starting from a Northern European experience, implementation of ERAS has spread to other parts of Europe including France, UK, Spain, Switzerland, Germany, and Italy as well as to North America and Australasia. It has also been implemented in developing nations in Asia and Latin America. The global nature of ERAS has been recognized with multicenter contributions to refining the perioperative process.

Today, ERAS protocols have been described in many major general surgical operations, with recent developments and implementations in other surgical fields such as orthopedic surgery, cardiothoracic surgery, and gynecology.

Initial Development of ERAS in Northern Europe

ERAS was first established by a group of academic surgeons from several Northern European nations meeting as the ERAS Study Group in 2001. The original Study Group consisted of leading surgical groups from United Kingdom (Ken Fearon, University of Edinburgh), Sweden (Olle Ljungqvist, Karolinska Institutet and Ersta Hospital, Stockholm), Denmark (Henrik Kehlet, University of Copenhagen and Hvidovre Hospital), Norway (Arthur Revhaug, University of Northern Norway and Tromsø Hospital), and the Netherlands (Martin von Meyenfeldt and Cornelius DeJong, University of Maastricht) [4]. This initial group of clinicians was concerned with bridging the gap between tradition and best practices in perioperative care. What initially began from literature reviews to improve elective colonic surgery outcomes with a protocol over time morphed into the international collaborative effort for education and research on perioperative care that has defined ERAS as we know it today [5].

The Scandinavian countries were among the first to establish enhanced after recovery programs. Professor Kehlet's research on elective colectomy was initially astonishing in significantly reducing length of stay. The Danish efforts began with what was then known as fast-track surgery in a small series of patients undergoing elective sigmoid resection [6]. The benefits of ERAS in elective colon patients were confirmed subsequently in an international multicenter collaborative effort [7]. As such, the Danish centers were among the earliest to test ERAS.

The ERAS Study Group built on the efforts of Professor Kehlet's work with subsequent trials at each of the five contributing academic institutions. The Study Group realized it was evident since the early 2000s, when the first consensus protocols were published on colonic and rectal surgery, that there were discrepancies between practice and best practices [8]. Even among individual contributing institutions, there was significant heterogeneity in the application of certain parts of the protocol. The collaborative efforts led to the development of a database to enroll all patients to not only measure patient outcomes but also to monitor levels of compliance with specific parts of the perioperative protocol. This served to highlight the discrepancies in each individual center to show areas for improvement. Today this forms the basis of the ERAS Audit Program to monitor each involved center, acknowledging that continued review and feedback results in better outcomes.

The efforts of the Dutch (Maastricht working group) in establishing ERAS into the Netherlands healthcare system are to be particularly commended here [9]. Whereas ERAS was previously typically attempted in single institutions, the Dutch were pioneers in implementing protocols on a national level. With the cooperation of the Dutch Institute for Health Care Improvement, a government-led organization, a total of 33 hospitals participated during a 5-year period from 2005 to 2009 [10, 11]. This large-scale study involved a third of all Dutch hospitals. The study demonstrated improvements in standard of care following elective colonic surgery in participating hospitals, as well as showing feasibility of implementation on national level.

ERAS in the United Kingdom

The United Kingdom (UK) has played a significant role in the early and continued embrace of ERAS. Since inception, Scotland has been a founding member of the ERAS Study Group and ERAS® Society. The late Professor Ken Fearon (University of Edinburgh) was one of the initial drivers of ERAS in the early 2000s. The first ERAS protocol published by the ERAS® Society was for elective colonic operations and was led by Professor Fearon [12]. Several of the initial ERAS® Society protocols also involved UK institutions. The UK Chapter of the ERAS® Society was formed in 2011 and formally adopted as the British Chapter of the International ERAS® Society in 2016. The establishment of this chapter aims to promote knowledge and disseminate research through regular updates and an annual conference.

Similar to the governmental effort by the Dutch researchers, the United Kingdom government also played a role in implementing ERAS within its National Health Service (NHS). With its perceived benefits of cost saving and achieving productivity gains in an era of austerity, ERAS has been adopted with enthusiasm by the NHS. Although there were localized accomplishments in colorectal, musculoskeletal, gynecological, and urological surgeries at the time, there was a lack of a unified effort to implement ERAS nationally. Recognizing the evidence and encouraging results from sev-

eral randomized controlled trials and systematic reviews, the UK Department of Health and Social Care's Enhanced Recovery Partnership Program (ERPP) were established in England and ran for 2 years between 2009 and 2011 [13]. Along with the early Dutch efforts, this government-led initiative is the first national systems-wide approach to establish ERAS. It delegated ERPPs to each of the individual NHS trusts with plans to change the processes in each participating center. Following the evident success of ERPP in England as well as consensus from experts in the field [14], ERAS protocols were subsequently established across the whole of the United Kingdom.

A national audit following the program introduction collected data from 24,513 surgical patients in colorectal, orthopedic, urological, and gynecological ERAS patients from NHS hospitals [15]. Findings of this study supported the notion that the success of ERAS arises from the whole protocolized pathway of care, rather than just from any individual aspects of the protocol. Colorectal and orthopedic surgery had the strongest association with decreased length of stay, with weaker evidence for gynecological surgery. This audit agreed with existing literature demonstrating the reproducible improvement in quality of care following standardization of healthcare processes [16]. Given the relatively recent national implementation of ERAS in the United Kingdom, evaluating the robustness of data on cost-effectiveness of the programs requires caution [17].

The efforts of the UK ERAS national implementation serve as an example for future nationwide efforts in promoting ERAS. Indeed, it highlights an example of the importance of securing high-level support. Although efforts of individual NHS trusts were instrumental in implementing protocols, it is evident that national support with funding, research, and coordination was indispensable in ensuring that targets were set and auditing was performed.

ERAS in Continental Europe

Although ERAS research, implementation, and publications were initially concentrated in Northern Europe as well as in the United Kingdom, there has been increasing research and implementation in continental Europe. Several publications since the 2010s have highlighted the efforts of continental European countries, such as in Spain, France, and Switzerland. Although by no means exhaustive, we highlight in this section examples of some of the efforts carried out by national ERAS organizations.

Similar to other countries that had implemented ERAS, what initially began as individual interests in implementation in Spain grew into interest groups, which in time morphed into a movement. In April 2008, the Grupo Español De Rehabilitación Multimodal (GERM or Spanish Multimodal Rehabilitation Group) was established with the main intent of collaboration and interest in implementing ERAS in Spain. The group grew and developed into the ERAS® Society for Spain, being the official ERAS® Society group in 2015. Their efforts have mainly been concentrated in Spain, but there has been a special interest in all Spanish-speaking countries internationally. GERM established national databases for which participating members could audit their practices.

Published nascent Spanish ERAS efforts began with elective colonic surgery. Observational studies in colon surgery demonstrated variability of compliance in fast-track programs, which at the time was implemented by each individual hospital unit [18]. A national elective bariatric surgery protocol was established by the Spanish ERAS® Society and successfully implemented in a pilot trial [19]. This subsequently was shown to have similar operative outcomes and complications when compared with a non-fast-track approach, with reduced postoperative pain and length of stay [20]. A national survey published in 2016 for Spanish surgeons and anesthetists reported familiarity with ERAS protocols but lacked overall consensus and adherence to existing guidelines [21].

ERAS in France is championed by the multidisciplinary Groupe francophone de Réhabilitation Améliorée après Chirurgie (GRACE or Francophone Group for Enhanced Recovery After Surgery), which also incorporated efforts in Francophone Belgium and Switzerland. GRACE was established in 2014, and similar to other independent national organizations, its aims are to promote the large-scale implementation of enhanced rehabilitation. GRACE, through its Web site, also functions as a repository of resources for any groups wishing to establish ERAS in their own centers. Each center subsequently is then enrolled as a "Centre GRACE" with access to all resources to help with implementation as well as participation in the data bank GRACE-AUDIT [22]. The GRACE-AUDIT works in a similar manner to the ERAS® Society Interactive Audit System in that it is both a data bank and auditing platform that supports continuous control.

Preliminary research into the large-scale efforts in implementation in France showed it was feasible and safe [23]. Colorectal, bariatric, and hip and knee orthopedic surgery in GRACE centers were initially implemented given their high levels of existing evidence and high volume of cases. Although ambitious, like all national-level programs, the Francophone evidence concurs with the literature [11, 15] that a nationwide effort is feasible in achieving improvements in patient outcomes. Economically, high-volume elective surgery with ERAS demonstrated significant cost savings for the French healthcare units [24].

ERAS in the United States

In Europe, knowledge of ERAS has increased among healthcare practitioners with increasing uptake in the past decade after numerous successful implementations in clinical practice. Since the 2010s, ERAS has also become increasingly utilized in the US healthcare system, with several centers initiating enhanced recovery programs. Despite best evidence, ERAS uptake in the United States has been slow [25]. Nongovernmental organizations such as the American Society for Enhanced Recovery (ASER) and the ERAS® Society USA Chapter are relatively new, being founded in 2014 and 2016, respectively. They work like their overseas counterparts, as drivers for research and promoting and implementing enhanced recovery programs.

In contrast to the national support and implementation of ERAS in many other countries, in the United States, there is a lack of a federal response to implementation. The lack of federal support is perhaps linked to the geopolitical and socioeconomic complexities of healthcare provision in the United States. The varying nuances of healthcare provision between each of the states and a multitude of different hospital systems all stand as a challenge to a national response to ERAS. There is a lack of published evidence of large-scale implementation of ERAS programs in the United States. One example of a systems-wide approach is in northern California, within colorectal and orthopedic specialties [26], demonstrating impressive results when working with a heterogeneous group.

Improving cost efficacy and decreasing hospital costs is one of the non-patient factors that makes ERAS programs attractive. The United States routinely has the highest health expenditures in the Organisation for Economic Co-operation and Development (OECD), and with unsustainably increasing expenses, there is a strong incentive in developing programs that can reduce costs. However, the expenses of implementing an ERAS protocol has been paradoxically mooted to contribute to the slow uptake of ERAS in the United States [27]. There have been several recent publications in the international literature describing the economic benefits of ERAS programs in Canada [28], Switzerland [29], and New Zealand [30]. New evidence from single-institution colorectal units employing ERAS in the United States has concurred with these international studies, demonstrating the reduced LOS and increased surgical turnover that translates into significant cost savings [31, 32]. Despite the studies being more cohort series rather than randomized controlled trials, the literature demonstrates that ERAS can provide healthcare savings within complex systems such as the United States.

With recent interest in the prescription opioid crisis that has afflicted the United States, there have been several publications investigating the role of ERAS programs in reducing opioid consumption. The United States currently consumes a staggering 80% of the world's supply of opioids [33], presenting a significant burden on patient morbidity and expenditure in the healthcare sector. While prescription opioids are not an issue isolated to the United States, they do present a substantial challenge to the US health authorities as well as other countries [34]. The emphasis on multimodal analgesia and decreased levels of systemic opioids with ERAS protocols could potentially deliver an opioid-free postoperative period, but available evidence is still inconclusive [35, 36].

ERAS in Other Developed Nations

ERAS acceptance and implementation as the standard of care has been predominately reported in the European setting. In this section, we discuss some of the contributions, successes, and lessons of ERAS in other developed nations, outside of Europe and the United States.

The efforts of the Canadian province of Alberta in establishing a province-wide ERAS program, beginning in 2013, in all relevant surgical procedures have been well described in recent literature (see Chap. 61). The Alberta Health Services is the largest fully integrated health system in Canada, providing universal coverage for 4.2 million people. It echoes previous economic studies that ERAS programs are cost-saving when evaluated against conventional approaches to perioperative care [37, 38]. Although initial evidence from the program involving colorectal patients demonstrated promising patient outcomes [39], the longer-term results still need to be closely scrutinized [40]. Initial compliance with the whole ERAS program has also been identified as an issue. The example in Alberta provides some guide to the global surgical community of the challenges and pitfalls in systems-wide implementation of ERAS [41].

Outside of Europe and North America, significant efforts in ERAS have been made in Australasia. New Zealand ERAS centers have been among the first internationally to publish fast-track protocols in colonic surgery [42]. New Zealand's National Orthopaedic Enhanced Recovery after Surgery Quality Improvement Collaborative was a nationwide program, which ran from November 2013 to March 2015, looking at implementing ERAS for hip and knee arthroplasty as well as managing patients with fractured neck of femurs. Published results have demonstrated improved patient clinical outcomes following implementation [43, 44] with recent official documentation demonstrating positive results [45]. ERAS in Australia is also becoming increasingly established with numerous published efforts to set up programs, primarily in orthopedic and colorectal surgery [46–48].

Japan has a universal healthcare system servicing a large population base. It has comparable general surgical outcomes on par with or exceeding those of many Western nations. ERAS programs for colorectal surgery have been

trialed in Japanese centers since 2010 but more recently have been modified to fit with traditional Japanese culture for general surgical procedures [49, 50]. Further studies are required to measure the effect of these modifications. The Japanese experience would serve as an example to the feasibility in non-Western countries but also the need to factor in culture differences in different populations.

ERAS in the Developing Nations of Asia, Africa, and Latin America

Although the concept of ERAS has been around for the last two decades, the majority of published ERAS experience has been concentrated in Europe, the United States, or in Anglophone countries such as Canada, Australia, and New Zealand. The benefits and limitations of ERAS programs in Asia, Africa, and Latin America have been detailed and explored in further details in earlier chapters of this book (see Chapters 62, 63, and 64). We highlight in this section some of the existing efforts made in these countries recognizing that the English literature is probably lacking in this area.

China and India are the regional and upcoming global, economic, and population powerhouses. Healthcare systems are heterogeneous in both nations. Despite the growing body of evidence, except for a few scattered and leading centers, a comprehensive response to ERAS is lacking [51–53]. Similar to the Japanese experience, these Asian nations also incorporate a culture where patients consider surgery to be associated with a prolonged period of stay, paradoxically presenting a barrier to earlier discharge [50, 54]. Programs are typically implemented in individual institutions, and there is no national program in place in either country. Promisingly, several organizations within each nation have developed in the last decade to promote ERAS.

South Africa is a major developing country in Africa. The perioperative effort in South Africa remains fragmented, and there does not appear to be a concerted effort between the various specialties to optimize this. ERAS has been identified as a national priority in surgical research [55, 56]. Bariatric surgery appears to be a success story in implementation in South Africa [57]. Published evidence on other African nations is scant. Given that the majority of ERAS protocols are simple and can be implemented without needing expensive equipment, as well as having significant potential cost savings, it presents an ideal opportunity for research in the African continent.

The Projeto ACERTO (ACEleração da REcuperação TOtal pós-operatória, Portuguese for Total Postoperative Recovery Acceleration) is part of the Brazilian effort to promote evidence-based perioperative principles as well as evaluating ERAS protocols to suit the Latin American healthcare setting. It is a multimodal educational tool based on ERAS protocols and aims to achieve what the ERAS® Society has promoted in Europe [58]. Initiated in 2005, the decade following implementation has shown demonstrable improvements in participating institutions, consistent with the international literature, in general surgery [59] and more recently in orthopedic surgery [60]. In 2017 A Latin American ERAS Chapter was formed; ERAS LatAm Society was established under the leadership of Adrain Alvarez (Argentina) with members also from Brazil, Chile, Colombia, Mexico, and Uruguay.

Global Collaboration Efforts

Collaboration has flourished through the widespread utilization of the various ERAS programs and societies. As an example, the ERAS® Society has collaborated with the European Society for Clinical Nutrition and Metabolism (ESPEN) and the International Association for Surgical Metabolism and Nutrition (IASMEN) a member society of the International Society of Surgery (ISS) to develop guidelines for perioperative care in rectal/pelvic surgery [61]. These guidelines highlight the need for collaboration to enhance the ERAS program.

The ERAS program has been successful throughout the world. The implementation of ERAS programs has allowed for collaboration between centers and countries. The ERAS® Society has an interactive audit and research tool that is updated prospectively by several centers in different counties. This approach has allowed collaboration and collective research into the effectiveness of the ERAS program in different settings. The ERAS compliance group has used this data to further knowledge about ERAS by examining which factors of the ERAS protocol most influenced outcomes [7]. Collaboration is also seen throughout the various ERAS programs, as evident by the publication of joint statements of the ERAS® and ERAS® USA societies [62].

Role of ERAS in World Health Organization (WHO) Global Surgery 2030

The WHO has identified 5 billion people who do not have access to safe and affordable surgical care when needed. There is a shortfall of 143 million additional procedures to meet the demand for surgery in low- to middle-income countries (LMICs). The shortfall can be met by significant investment as well as reduction in costs of surgical care. ERAS program implementation in LMICs can help in improving outcomes and reducing costs by reduction in morbidity, mortality, and length of stay [37].

The ERAS principles provide LMICs with an opportunity to standardize and audit care on a large scale. There is potential for healthcare savings as well as better patient care. The

global focus on surgery in the WHO 2030 plan provides a unique opportunity to build efficient protocols for anesthetic and surgical care using the ERAS principles. Components of the ERAS program will ensure important expertise, and essential medicines are available, as in the case of locoregional anesthesia. The protocol will also ensure that unnecessary treatments, such as drains or overuse of intravenous (IV) fluids, are minimized.

ERAS principles tie in well with the WHO Global Health vision 2030. These protocols have a potential to improve care at a reduced cost by focusing on preoperative optimization, available cost-effective medications (e.g., antibiotics), regional blockade, multimodal analgesia, and early mobilization [63].

Conclusion

Improved evidence-based perioperative care, promoted on the ERAS platform, provides a widespread appeal to the global surgical community. Over the last two decades, interest and implementation of ERAS protocols have spread from Eurocentric academic institutions to centers across both the developed and the developing world (Fig. 65.1). With improvements in both individual patient outcomes and increased healthcare cost efficiency, ERAS programs prove attractive in a wide range of settings. In many nations, ERAS still remains in its early stages of implementation to establish itself as the standard of perioperative surgical care, providing an exciting opportunity for the future.

Future Direction and Research in the Field

Although ERAS has been around since the late 1990s, the uptake of programs in many countries has been relatively recent. Given this new field of perioperative care, there is a large scope for future research.

Currently there is a lack of literature from non-Anglophone nations, especially those in developing nations that have yet to establish or have recently established ERAS programs. This provides an ideal opportunity for research in ERAS implementation and outcomes in countries outside of Europe and North America. Outside of a few examples in the United

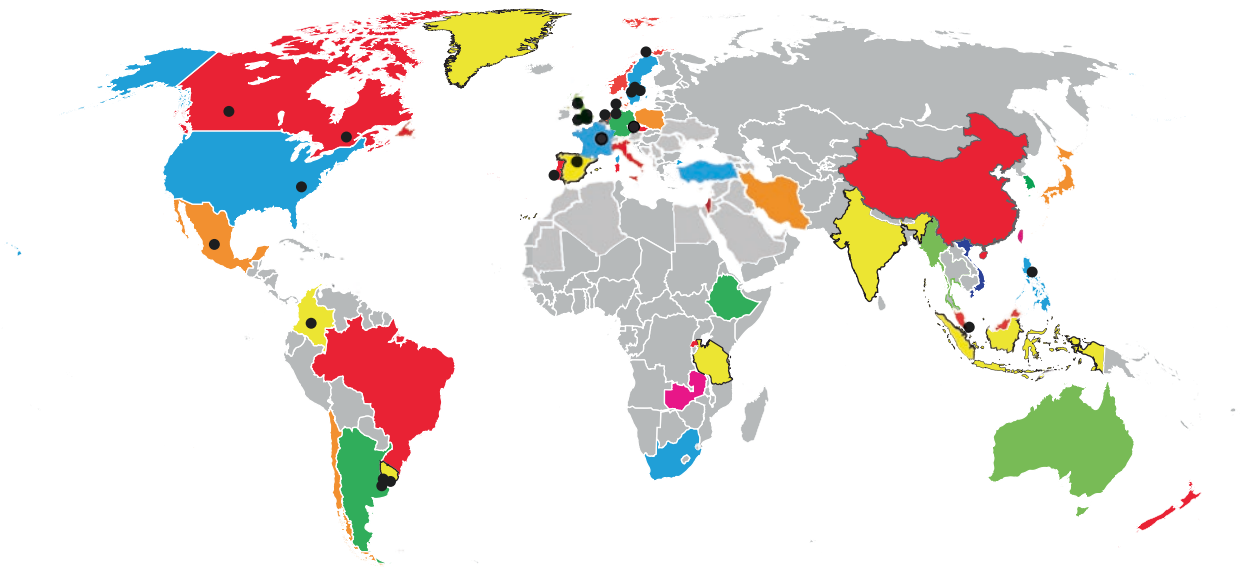

Fig. 65.1 Global spread of ERAS is shown with color on the map. ERAS® Society Centres of Excellence are shown as black dots

Alberta Health Services, Alberta, Canada
Carolinas Medical Center, Charlotte, USA
Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland
Centro de Asistencia Médica del Oeste de Colonia (CAMOC), Carmelo, Uruguay
Clínica Reina Sofía, Bogotá, Colombia
Danderyd Hospital, Stockholm, Sweden
Edouard Herriot Hospital, Lyon, France
Ersta Hospital, Stockholm, Sweden
Hospital Beatriz Ângelo, Lisbon, Portugal
Hospital Civil, Guadalajara, Mexico
Hospital de Italiano, Buenos Aires, Argentina
Hospital Universitario "Lozano Blesa," Zaragoza, Spain
Maastricht University Hospital, Maastricht, Netherlands
Martini General Hospital, Groningen, Netherlands
McGill University Health Center, Montreal, Canada
Medica Uruguaya, Montevideo, Uruguay
Örebro University Hospital, Örebro, Sweden
Royal Surrey County Hospital, Guildford, United Kingdom
St. Mark's Hospital, London, United Kingdom
Tan Tock Seng Hospital, Singapore
The Medical City, Manila, Philippines
University Hospital Hamburg-Eppendorf, Hamburg, Germany
University Hospital of Northern Norway, Tromsø, Norway
The University of Edinburgh, Edinburgh, Scotland
Yeovil District Hospital, Yeovil, United Kingdom

Kingdom, the Netherlands, and Canada, there is still relatively little evidence present for the effects of systems-wide implementation of ERAS. Future directions of research should examine the patient and healthcare economic impact of system-level implementation, which could yield new information on successes and pitfalls.

Furthermore, given the relatively new nature of ERAS, there is a role to play in studying the long-term outcomes of ERAS in nations that have already established ERAS. This could provide further information and incentive for nations wishing to present a case for long-term health benefits.

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