Personalized Medicine in Anesthesia, Pain and Perioperative Medicine

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Preface

As anesthesiologists, we need to help predict the risk for individual patients for specific surgeries and/or procedures. Although these physicians are aware of randomized clinical studies that suggest specific outcomes for those individual patients, there are some very important problems with the clinical studies that are available. What needs to be remembered is that the "use of evidence from clinical trials to support decisions for individuals" is a form of "reference class forecasting": implicit predictions for an individual are made on the basis of outcomes in a reference class of "similar" patients treated with alternative therapies. Yet, often patients are excluded because they have a low event rate or for other reasons—making the study population unlike the patients we care for. The goal of personalized medicine is to narrow the reference class so that the patients studied are more similar to the patients we care for.

This is clearly not the case in multiple clinical trials, where patients of different ages with multiple problems are compared to those who have no or few problems. It appears that even our randomized clinical trials truly lack the ability to predict outcomes for many of our patients and that even the statistics utilized may be inappropriate. An example of this problem is that testing for the null hypothesis in critical care studies has led to multiple negative studies; yet, using Bayesian analysis documented the utility of therapies in patients on ECMO while testing for the null hypothesis did not.

This book evaluates how to better predict perioperative outcomes for our patients by personalizing our analyses—and methods to improve our predictions. Clearly, this is important as we undertake to anesthetize more patients, including our sickest patients.

Boston, MA — Jeanine Wiener-Kronish

Preface

Today, world's problems are more complex than before; at the same time, these dilemmas need novel solutions with these specifications: creative, multifaceted, intelligent, and evidence-based approaches. Meanwhile, world health challenges have shifted dramatically.

During the last few years, scientific improvements in medicine have soared up. This is in part due to the scientific improvements; however, the paradigm shift in medical research has a great role. Nowadays, interdisciplinary research has more pronounced position. The application of artificial intelligence, cellular and molecular techniques, tailoring diagnostic, therapeutic, and prognostic approaches for each person, and formulating individual solutions for each human being are among the most important perspectives of today's medical research.

Personalized medicine, a creative approach in today's medicine, has come out of the heart of this revolutionary research approach. Anesthesiology and perioperative medicine is one of the fields of medicine that would best fit the personalized medicine approach. Issues like tolerance to pain, organ system function during anesthesia and after that, optimization and prehabilitation of the body for coping with the perioperative stress response and the personalized reaction to stress response, tailoring analgesic regimen for each patient in both acute and chronic pain, selecting anesthetic drug based on individual patient characteristics, profiling the possible allergic and anaphylactic response of each patient based on his or her immune system, and many other aspects of the clinical care in anesthesiology and perioperative medicine are best examples of appropriateness for clinical use of personalized medicine.

However, the road from "bench to bedside of anesthesiology and perioperative medicine" is still at some points under construction. The current research fields of multi-OMICS has very well-endorsed anesthesiology and perioperative medicine; though some areas are still developing. This is at many times just not a matter of research; instead, many aspects are incorporated in practice and it is anticipated to be a developing feature of anesthesiology; in such a way, using the word "anesthesiomics" would be a real possibility in the near future. The main hindrance in this path is the issue of available technology all over the clinical field and also the

challenges of expense. However, with the stunning speed of technology development, the latter issues seem to be fading in future years and using multi-OMICS techniques in anesthesiology and perioperative medicine would be a completely tangible reality.

This book includes 17 chapters focusing on personalized anesthesiology and perioperative medicine with the starting chapters discussing the more basic principles, and in the following chapters, organ- and system-based approaches have been incorporated. Separate chapters on pediatric and elderly populations have been written to encompass the specific considerations in these age-specific populations. The last chapter discusses the principles in medical education in order to perform a curriculum transition to a novel personalized anesthesia and perioperative medicine one.

The ultimate goal of health care is to enhance the outcome and impact of our efforts in saving lives and improve quality of lives. Personalized anesthesia and perioperative medicine could be a smart approach for anesthesiologists and perioperative medicine specialists to reach this goal; especially in the era of multi-OMICS medicine.

This work could not be published without the incredible scientific efforts of all contributors. However, I have to express my especial gratitude to Dr A. Sassan Sabouri, Assistant Professor, Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, USA. I am highly appreciative of his generous kindness in contacting a number of the contributors and following them up.

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Tehran, Iran Ali Dabbagh

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Chapter 1
The Role of Personalized Medicine in Current and Future Clinical Practice of Anesthesiology and Perioperative Medicine: Towards Anesthesiomics

Ali Dabbagh and A. Sassan Sabouri

Introduction

Anesthesia is a medical invention lasting less than 2 centuries. Physicians at that time invented anesthesia due to an inevitable need of physicians who could not proceed a major number of treatments without controlling intolerable pain of their patients. However, during the forthcoming decades, anesthesia grew up; then was transformed from a simple technique application to a branch of medicine often known as "Anesthesiology and Perioperative Medicine" or succinctly as "perioperative medicine". This trend did not stop in the clinical stage; it grew up towards cellular and subcellular aspects of medicine to create a new feature of anesthesiology (Naguib et al. 2012; Dabbagh and Elyassi 2016; Dabbagh 2017; Iravani et al. 2017; Kim et al. 2018; Odell 2018).

In the current era, perioperative medicine has been privileged by domains of care; each including a long list of activities:

- Preoperative care
- Intraoperative care
- Postoperative care

On the other hand, during the last years, especially the last 2 decades, a combination of multiple approaches has revolutionized medicine. The goal of this "novel doctrine in medicine" is to tailor medicine for each human being; simply talking, like fingerprint which is individual-proof. Besides, this is a real and basic shift

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"from reactive medicine to preventive medicine"; taking preventive approaches with a strategic look forward instead of a "wait and watch" approach. However, this approach known as personalized medicine has been mainly granted by the following scientific and/or practical developments:

- genome sequencing and its related techniques
- development of detailed list of cellular and molecular disciplines in medicine; from bench to bedside, creating many—OMICS fields; including but not limited to genomics, epigenomics, transcriptomics, proteomics, metabolomics, interactomics and so on (Topol 2014; Tebani et al. 2016; Donovan et al. 2019; Wolfender et al. 2019; Dabbagh 2020)
- artificial intelligence and big data management (Krittanawong et al. 2017; Schork 2019; Hashimoto et al. 2020)
- involvement of industry in genomics and related sciences (e.g. pharmacogenomics)

Other names have been coined for this medical doctrine; e.g. precision medicine, P4 medicine (predictive, preventative, personalized, participatory) and Theranostics (Flores et al. 2013; Lu et al. 2014). Though they have been used interchangeably, their definition is not necessarily the same. One of the most important applications of personalized medicine is to create and/or optimize the pathways that can predict and plan the health/disease pattern for each person in prevention, diagnosis, treatment, mortality, risk assessment and prognosis based on that person's whole biological data (i.e. —OMICS data) (Topol 2014; Tebani et al. 2016; Donovan et al. 2019; Wolfender et al. 2019; Dabbagh 2020).

In order to review part of the related evidence, a number of clinical applications of personalized perioperative medicine are listed in Table 1.1; the list will be ever increasing with many aspects of the perioperative care being personalized.

In this chapter, a brief overview on the impact of personalized medicine in the main steps of perioperative care is provided; having a general look on the current and future aspects of clinical practice. However, more detailed discussions could be found throughout the book chapters.

Preoperative Care

The main goal for preoperative care is to prepare the patient for tolerating the stress of the surgery or other medical interventions and treatments which are part of the process of controlling the underlying disease; in such a way to optimize the underlying condition and to improve the overall outcome. However, there are always barriers to achieving this goal and the strategy to achieve this goal should be tailored case by case.

Preoperative evaluation is the first step in delivering care by anesthesiologists more than any other time. Not only the medical status of the patient should be optimized but also the psychological, behavioral, economic and societal factors of the

Table 1.1 some clinical applications of personalized perioperative medicine

Preoperative care: • preoperative risk prediction scoring based on personalized models • preoperative prediction of in-hospital and out of hospital mortality and morbidity based on personalized models • preoperative assessments for pharmacologic tailoring (including the anesthetic implications of pharmacogenomics) • management of clinical scenarios with major pharmacological interaction • perioperative acute and chronic pain management; designing a personalized model for pain management • postoperative nausea and vomiting control using a personalized model • perioperative antibiotic choice; perioperative management of septic/infectious complications using a personalized model • intraoperative tailoring of anesthetics, including personalized model of drug selection for hypnosis, amnesia, muscle relaxation and analgesia and also, personalized management of their potential complications/side effects • perioperative protection of organ systems (inflammatory mechanisms, ischemic insults, etc.) • management of vulnerable patient populations (geriatric, infancy, childhood, pregnant mother) • personalized preoperative optimization of patients for the surgery; monitoring patient status using –OMICS markers
Intraoperative care • anesthetic drug choice and dose • intraoperative organ monitoring • intraoperative organ protection • hemodynamic optimization • management of potential intraoperative complications like malignant hyperthermia • intraoperative blood management and transfusion • intraoperative infection control • intraoperative safety management
Postoperative care • postoperative acute and chronic pain management • postoperative nausea and vomiting • hemodynamic management • coagulation and bleeding management • respiratory monitoring and management • management of residual anesthetic drug effects with focus on personalized aspects of anesthetic drug metabolisms • postoperative management of neurologic and psychiatric dilemmas

patient and his/her family should be considered (Fleisher 2018). This process is not just a matter of medical prescription; instead, active participation of the patient side (including the family) has a pivotal role.

However, based on a traditional approach, the first step is to perform an organ system-wide assessment of the patient, mainly focusing on phenotype and the effects of surgery or underlying disease(s) on phenotype of the patient. Besides, clinical history of using any pharmaceutical or other drugs (including any history of drug abuse or smoking) is regularly assessed. A number of patient groups need higher vigilance levels, including the pregnant mother and her fetus, the elderly and children/neonates. Acute and chronic pain management is another integral part of

preoperative care that should be tailored for each patient. In the era of ERAS (Early Recovery After Surgery), preoperative evaluation and optimization have gained much more attention. In the majority of the patients, a battery of preoperative testing is added to the clinical assessment.

Recent studies have suggested the latter traditional assessment is not enough; not only regarding lab tests, but also in order to improve the models of preoperative optimization through personalized medicine approach. In fact, for each patient, his/her individualized path for overcoming the perioperative period and management of its potential complications should be tailored (Dabbagh and Rajaei 2016; Gabriel et al. 2017, 2018, 2020; Aroke and Hicks 2019; Harris et al. 2019; Kaye et al. 2019).

Pharmacogenetics (PGx) or the study of hereditary drug metabolism is one of the key components of personalized medicine. Using Pharmacogenetics data may enable practitioners to target appropriate patient or patients' papulation for the best outcome. PGx is based on the assumption that genetically supported targets are more likely to succeed for treatment. Many studies have been implicated perioperative personalized medication, but the higher quality and more evidence-based studies are needed to make a more pronounced and effective chance in perioperative practice in specific individuals (Saba et al. 2017). A comprehensive and up-to-date resource of our current knowledge about the relation of genetic variation and how our body responds to medication is available in many robust sources like PharmGKB (https://www.pharmgkb.org/) and Pharmacogenetics Research Network (https://www.pgrn.org). Clinical pharmacogenetics implantation consortium publishes guidelines and evidence-based evaluation related to using PGx tests for patient care.

Using Electronic Health Records (EHR) enables recoding of patient's medical and health history longitudinally. EHR has a widespread adoption over the last 15 years in the USA and more than 97% of all hospitals in the USA has adopted *Certified* EHRS in 2014. EHR has generated a vast and continuously growing resource that can enable large scale research. With recent combination of EHR and Genomics Network (*e*MERGE network) has opened another window to personalized medicine. *e*MERGE is a National Institute of Health (NIH)-organized and funded consortium that develops researches combining bioinformatics with EHR for genomic discovery and precision medicine implementation. With eMERGE phase III expansion, a total of 10 websites are involved with developing and validating electronic phenotyping algorithms in order to incorporate large-scale genomic researches in one common source. eMERGE is a great source for EMR and Biorepository Information; while providing sufficient data. The structure of eMERGE includes the following:

- Investigative Sites
- Centralized Sequencing and Genotyping (CSG) Facilities
- Coordinating Center (CC)
- External Scientific Panel

A detailed list of the Participants and Structure of eMERGE could be found at https://www.genome.gov/Funded-Programs-Projects/Electronic-Medical-Records-and-Genomics-Network-eMERGE

Intraoperative Care

This period of care is part the continuum of perioperative medicine with especial considerations. The hallmark of intraoperative care is the relatively exceptional status of the patient; being anesthetized or under anesthesia care and the therapeutic procedure.

Throughout the last decades, there are a number of turning points and/or important events that have affected the intraoperative anesthesia care:

- the increasing trend for monitoring vital organs; especially in the vulnerable patient groups
- the robust evidence in favour of improved outcome due to more sophisticated monitoring of the patients
- much more targeted anesthetic drug designs with fewer side effects and increased efficacy and safety
- preventive strategies to improve the quality of care throughout the surgery (like prevention of organ ischemia, prevention of patient awareness, pre-emptive analgesic approaches, perioperative stress response modification, preventive measures form intraoperative infections and contaminations, etc.)

The trend of improved quality of intraoperative anesthetic care would be undoubtedly thrived using the developments by personalized medicine. Although the price of delivering personalized anesthesia care is still too high to afford, the development in technology during the next years would change the pattern in such a way that these would be affordable in our daily clinical practice (Iravani et al. 2017).

Postoperative Care

Personalized medicine could be a highlighted aspect of care from the entry point of the patient to the postoperative care area (PACU or ICU); starting but not limited to those presented in Table 1.1. The fact is patients undergoing postoperative period do not experience the same; mostly due to the personalized differences in the postoperative effects of anesthesia and surgery. Optimization of patient care through personalized approach would improve the quality of care in postoperative period.

Personalized Anesthesia: A Reality in Daily Practice

As a matter of fact, personalized anesthesia in essence aims to “tailor” medicine for each human being. So, the core concept is not bizarre or far from the goals of treatment so far. However, within the last 2 decades, the revolutionary scientific progress in medicine has made it available to tailor medicine for each human being based on cellular and subcellular mechanisms; i.e. using the —OMICS approach (Gerstein

et al. 2014; Jimenez and Galinkin 2015; Tebani et al. 2016; Iravani et al. 2017; Olivier et al. 2019; Dabbagh 2020).

In fact, the hallmark of this novel school of thought in medicine is adding a point-by-point correlation between genotype and phenotype of each person, both in health and disease. This is not just as simple as previous ones; instead it has created a paradigm shift in many branches of medicine (Tebani et al. 2016; Sezari and Dabbagh 2019). The same is correct for anesthesia and perioperative medicine. Having point of care—OMICS tests in the operating room or before and/or after that is not far from access in near future; while in some aspects, it could be nowadays available. The only remaining things are the matter of time and the expense; both would be resolved within the next couple of years due to inevitable scientific and technical developments. Possibly it is not too far to hear the words "anesthesiomics"or "personalized anesthesia and perioperative medicine" once considered a bit more than a "pipe dream" would be a common clinical word in our day to day practice. Just at a glance! (Bruehl 2015; Stary et al. 2015; Iravani et al. 2017; Knezevic et al. 2017; Kaye et al. 2018; Donovan et al. 2019; Dabbagh 2020).

Personalized Medicine Is Not the Answer for Everything

It is essential to know the personalized medicine pitfalls and restrictions. For instance, the effect of public health interventions such as smoking cessation, although does not fall in any categories of personalized medicine, still is a valid prevention toll in any health system. The relationship between genes and phenotypes are not always clear as environment, exposures, and lifestyle can all influence genetic expression.

In the two medical disciplines that represent the largest cause of morbidity (i.e. oncology and cardiology) personalized therapeutics has yet to show the hoped-for salient changes in clinical outcomes (Dugger et al. 2018). Cost of genetically based research and treatments is another barrier of using precision medicine, especially in the perioperative setting. However, without reservation, personalized medicine has opened a new, real and tangible horizon in the medical field.

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Chapter 2
The Role of OMICS (Genomics, Epigenetics, Transcriptomics, Proteomics and Metabolomics) in Personalized Anesthesia and Perioperative Medicine

Samira Mohammadi-Yeganeh, Slawomir Bilanicz, and Ali Dabbagh

Introduction

The practice of anesthesia has evolved as an art and a science, but is far from perfect due to the unpredictability and heterogeneity of individual patient responses (Galley et al. 2005; Dabbagh and Elyassi 2016). These differences lead to unpredictable responses or toxic effects in individuals or sub-groups, and can ultimately affect patient outcomes. A priori identification of susceptible individuals could lead to modification of drug dosage or use of an alternate drug, which might prevent these serious adverse drug reactions (SADR) (Palmer et al. 2005).

Annually, 234 million surgical procedures are carried out. It is estimated that seven million patients experience harm that up to 50% of this harm is avoidable, in addition one million die each year post-operatively worldwide (Weiser et al. 2008).

Mortality rates across 28 European countries were examined in 2012 European Surgical Outcomes Survey and results show that in the UK cohort there was a 3.6% mortality rate following non-cardiac surgery (n = 10,630). In 2014, just 15,460 patients participated in National Audit Project Activity Survey and received general

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anesthesia. Of this cohort, nine patients died, representing a 0.06% intraoperative mortality rate (Sury et al. 2014). In recent decades, an improvement in anesthesia related factors and safety causes reduction in surgical mortality rates (Schiff et al. 2014).

The publication of the human genome in its entirety in 2003 signaled a new dawn in the quest for a greater and more complete understanding of the variations which govern genes and the proteins which they express. Much of the promise and potentials of the human genome project remains to be developed and seen; however, the entry of medicine to the post-genomic era lead to greater advances in rapid DNA sequencing technologies. It is anticipated that the knowledge gained from the human genome project will be instrumental in advancing developments in pharmacogenetics and personalized medicine (Collins et al. 2003).

Pharmacogenetics and pharmacogenomics are distinct entities which are often used interchangeably in medical literature (Ama et al. 2010). *Pharmacogenetics* refers to the study of variability in an individual's response to a drug due to heritable factors (Ama et al. 2010). *Pharmacogenetics* evaluate the association of single nucleotide polymorphisms (SNPs) with how individuals metabolize drugs. Pharmacogenomics is a broader term which may be regarded as:

- the application of pharmacogenetics to the whole genome and across populations, encompassing proposed outcomes such as generating drug response profiles unique to each individual based on their genetic make-up (Morris-Rosendahl and Fiebich 2004)
- examining the effect of drugs on gene expression (Xu et al. 2005)
- the eventual utilization of genomic principles in the development and trialing of new drugs (Harper and Topol 2012)

History of Pharmacogenetics (PG) & Anesthesia

William Bateson coined the word 'genetics' in 1905 (Cock 1973). In 1909, Archibald Garrod proposed the concept of inter-individual differences in drug response in his book 'The Inborn Errors of Metabolism'. Though the role of barbiturates in precipitating acute porphyria was first established in 1937, the dawn of modern genetics was born after the Second World War in the 1950s. In 1952, about 17 cases of prolonged apnea after succinylcholine were reported (Birch et al. 1956). Kalow et al. are often credited with identification of a gene-variant of cholinesterase with reduced activity in patients with prolonged apnea (Kalow et al. 1956; Kalow and Gunn 1957). In 1959, Vogel coined the term "pharmacogenetics" for this new field of research (Motulsky 1957). *Roy Evans* was the first patient who survived malignant hyperthermia. After undergoing local anesthesia for appendectomy due to a family history of deaths under anesthesia, he underwent thiopentone/halothane anesthesia for a compound fracture of the leg after the anesthetist ruled out porphyria (Denborough et al. 1962). Despite these successful discoveries, about 20 years passed before the structure of serum cholinesterase and the ryanodine

receptor variant were actually elucidated. The last couple of centuries have been revolutionized by the implementation of the U.S. Human Genome Project. This was a 13-year effort coordinated by the U.S. Department of Energy and the National Institutes of Health. The project originally was planned to last 15 years, but rapid technological advances accelerated the completion date to 2003, resulting in elucidation of the 2.85 billion nucleotides that make up the human genome, and encode about 20,000 to 25,000 genes (Imagawa et al. 2004). Nowadays, the US Food and Drug Administration (FDA) has approved pharmacogenetic/genomic information/warnings in the labels of over 100 drugs, which include analgesics like codeine, tramadol/acetaminophen combinations and celecoxib.

Genetics and Pharmacokinetics of Anesthetics

Drug pharmacokinetics can be affected by genes through:

1. altering the *enzymes* that are responsible for drug metabolism and hence drug disposition
2. the *transport proteins*, which influence drug absorption, re-distribution and bioavailability

Phase 1 (Cytochrome P450 enzymes, cholinesterases) and the Phase 2 enzymes (Uridine Glucuronosyltransferases or UGTs and N-acetyl transferases) are the major groups of enzymes which catalyze metabolism of the majority of anesthetics commonly used (Chidambaran et al. 2012). The effects of gene variants on drug metabolism and clinical consequences are listed in Table 2.1.

Table 2.1 Effect of genetic variants on anesthetic/analgesic drug pharmacokinetics

Gene	No. of variants	Major variants	Consequences on enzyme activity	Examples of clinical consequences for anesthetic drug effects
CYP1A2	>20	*1F (−163C > T) *1 K (−739 T > C, −729C > T, −163C > T)	Increased after omeprazole	No in vivo clinical significance has been demonstrated
CYP2B6	>28	*6(516G > T, 785A > G) *16 *5 (172H–262K–487C)	Decreased	Increased risk of prolonged QT interval after methadone use in *6/*6 variant due to reduced metabolism *6 variant associated with methadone related mortality *5 haplotype associated with decreased propofol clearance

(continued)

Table 2.1 (continued)

Gene	No. of variants	Major variants	Consequences on enzyme activity	Examples of clinical consequences for anesthetic drug effects
CYP2C9	>30	*2(430C > T) *3(1075A > G)	Decreased	*2,*3 variants had reduced metabolism and increased action of ibuprofen in Spanish patients *2,*3 variants associated with higher anticoagulation from warfarin Increased risk of bleeding from Non-steroidal Anti-Inflammatory Drugs in *2, *3 variants
CYP2D6	>100	*3–*8, *11–*16, *19–*21, *38, *40, *42 (inactive) *1, *2, *35 (Functional/ wild-type) *9, *10, *17, *29, *36, *41 (decreased activity)	2 Nonfunctional alleles (PM) – 1 reduced functional allele or 1 active allele (IM) – 1 or 2 functional alleles (EM) or Multiple functional alleles (UM) in the absence of inactive or decreased activity alleles	Tramadol requirement after abdominal surgery higher in PM phenotype UM have increased incidence of ondansetron and dolasetron failure for postoperative vomiting Reports of death after codeine therapy in a breast-fed infant of UM phenotype mother and a 2-year old boy after tonsillectomy
CYP2E1	>13	*5 (−1293G > C, −1053C > T)	Increased	Tendency for halothane hepatitis to cluster in families, genetic mechanisms unelucidated
CYP3A4/5	>50	CYP3A4*1B CYP3A5*3 CYP3A4*1G	Increased Non-functional Decreased	Combination of CYP3A4*1G and CYP3A5*3 variants was associated with increased fentanyl analgesia in Chinese women after gynecologic surgery
UGT1A9	>100	D256N	Decreased	In vitro study indicated increased risk of propofol adverse effects
BChE	>30	A variant (209A > G) K variant (1615G > A)	Reduced metabolism of succinylcholine/ mivacurium	Prolonged duration of apnea in variants

Phase 1 Metabolism of Genes/Enzymes

CYP genes code the Cytochrome P450 (CYP enzyme) super family which are the major enzymes in the liver. Amino acid sequences determine the nomenclature of this group of enzymes and genes. There is 40% similarity in sequence between members of the same family and they are characterized by the number. *CYP1, CYP2 and CYP3* are the majority of relevant genes. Enzymes in the same subfamily have more than 55% similarity and identified by an alphabet (*e.g. CYP2D*). The number following the alphabet indicates the individual enzyme (e.g. *CYP2D6*). The number after the asterisk indicates the allele variants (i.e. *CYP2D6*1*) (Garte and Crosti 1999).

Nomenclature of polymorphic alleles of 22 CYP isoforms including more than 200 functionally different variants are covered in allele Nomenclature Committee website (www.imm.ki.se/CYPalleles/). The high variability and polymorphism of the CYP genes cause 4 major enzyme activity phenotypes. Depending on drug conversion into active or inactive metabolites by CYP enzyme, the action on drug effect would differ for the same genotype (Ma and Lu 2011). We discuss below the most important features of clinically relevant CYP enzymes that play a key role in the PK of anesthetic drugs only. A list of the genes affecting the PK of commonly used anesthetics is presented in Table 2.2.

CYP2B6 is one of the most polymorphic CYP genes. The ***CYP2C*** subfamily consists of four genes—*CYP2C8, CYP2C9, CYP2C18 and CYP2C19*. Of these, *CYP2C9* is the major hepatic enzyme and accounts for 18% of total CYP enzymes (Shimada et al. 1994). Warfarin, the most common drug mentioned in pharmacogenetic studies, is metabolized by *CYP2C9* and Vitamin K-epoxide reductase complex enzymes (VKOR-1) (Guessous et al. 2009). Various identified SNPs of *CYP2C9* and *2C8* are related to pharmacokinetics of non-steroidal anti-inflammatory drugs (NSAIDs) and anticoagulants (Lopez-Rodriguez et al. 2008; Ali et al. 2009).

CYP2D6 is the only non-inducible CYP enzyme, thus genetic variation determine difference in the enzyme activity (Bertilsson et al. 1993). The most common variants are *CYP2D6* *1, *2 and *10. While the wild-type is characterized as an Extensive metabolizer (EM), variant phenotypes are classified as poor, intermediate and ultra-rapid metabolizers (PM, IM and UM respectively) arising from genotypes formed by various combinations of alleles (Kaiser et al. 2002). In the Africans and Oceanians gene duplication or multiplication of *CYP2D6* is a common phenomenon. Algeria and North Africa show the highest prevalence of UM phenotype (Kaiser et al. 2002). Genetic variants are associated with altered phenotypes for the metabolism of anti-emetics like ondansetron as well as opioid analgesics like codeine, tramadol, hydrocodone and oxycodone (Stamer et al. 2003; Susce et al. 2006; Kirchheiner et al. 2007).

Table 2.2 Important genes and variants affecting anesthetic/analgesic drug pharmacokinetics

Genes	Inhalation agents	Non-opioid IV agents	Opioids	Nsaids	LA	Others	Muscle relaxants
CYP2B6		Ketamine Propofol	Methadone Meperidine Tramadol Hydromorphone				
CYP2C8		Midazolam		Diclofenac			
CYP2C9			Hydromorphone	Ibuprofen Diclofenac Naproxen Indomethacin		Warfarin Phenytoin Clopidogrel	
CYP2C19		Diazepam Midazolam Phenobarbital		Indomethacin		TCA, SSRI MAOI, PPI	
CYP2D6			Codeine Tramadol Hydrocodone Dextromethorphan Oxycodone Dihydrocodeine			Ondansetron Dolasetron Palonosetron Tropisetron Amitryptiline	
CYP2E1	Halothane Sevoflurane Desflurane Isoflurane					Acetaminophen Caffeine	

CYP3A4	Halothane	Ketamine Propofol Midazolam Diazepam	Morphine Meperidine Fentanyl Sufentanyl Remifentanil Alfentanil Methadone Codeine Buprenorphine		Amide group	Granisetron Ondansetron Dolasetron Palonosetron Tropisetron Domperidone Hydrocortisone	
CYP3A5		Midazolam Diazepam	Fentanyl Sufentanyl Remifentanil Alfentanil			Ondansetron	
UGT1A1		Lorazepam	Morphine			Acetaminophen	
UGT1A9		Propofol					
BChE					Ester group		Succinylcholine Mivacurium

CYP3A, located on chromosome 7q21.1, is the most abundant and clinically important subfamily is consisting of these important genes: *CYP3A4, CYP3A5 and CYP3A7*. *CYP3A4* accounts from 10–40% of all CYP enzymes though most of them are rare with no impact in alteration of the enzyme activity. It seems that *CYP3A4* induction and inhibition by medications or environmental factors is responsible for large variability of this gene without phenotypic polymorphism (Restrepo et al. 2009). *CYP3A5* is the primary enzyme of the *CYP3A* subfamily found outside the liver and intestine while *CYP3A7* is the predominant CYP enzyme in fetal liver (Chidambaran et al. 2012).

Phase 2 Metabolism Genes/Enzymes
UDP-Glucuronosyltransferase (UGT)

UGT (uridine 5′-diphosphoglucuronic acid) uses UDP for glucuronidation of hydrophobic compounds to convert them to more hydrophilic before they eliminate from the body. This major metabolic pathway carries out about 15% of drug clearance in humans. Two families, the *UGT1* and *UGT2* are identified based on the similarity of gene sequence. There are nine functional genes including *UGT1A1, 1A3, 1A4, 1A5, 1A6, 1A7, 1A8, 1A9* and *1A10* in the *UGT1* family, which are located on chromosome 2q37. *UGT2* family consists of eight genes, including *UGT2A1, UGT2B4, 2B7, 2B10,2B11, 2B15* and *2B28* are located on chromosome 4q13 to 13.2 (Tukey and Strassburg 2000).

Glucuronidation of morphine to morphine-3-o-glucuronide (M3G) and morphine-6-o-glucuronide (M6G) is done by *UGT2B7*. One-third of the Caucasian population have the most common allelic variant, *UGT2B7*2* (802C > T) which has not been found to impact morphine glucuronidation. It is in linkage disequilibrium with the −161C/T promoter variant whose T/T genotype was found to be associated with lower morphine levels in plasma compared to metabolite levels, while the wild type (C/C) had lower M3G and M6G levels (Sawyer et al. 2003). In children receiving morphine perioperatively, African-Americans showed higher morphine clearance than Caucasians and that common *UGT2B7*genetic variations (−161C > T and 802C > T) were not associated with observed racial differences in morphine's clearance although the wild type of the *UGT2B7* isozyme is more prevalent in the African-Americans (Sadhasivam et al. 2012).

Intravenous Anesthetics

Propofol is one of the most commonly used intravenous anesthetics. It acts *via* the GABAA receptor, which has no preference to specific subunits. *CYP2B6* enzyme hydroxylatePropofol and then it undergoes O-glucuronidation by *UGT1A9* (Court

et al. 2001; Zanger et al. 2007). At secondary cascade, 4-hydroxypropofolis produced by *CYP2C9* that is further metabolized by enzymes DT-diaphorase (NQ01) and sulphotransferase, or conjugation (Li Lin et al. 2006; Restrepo et al. 2009). Bradycardia (incidence-5-23%), asystole (1.9–15 per 15,000 patients) and propofol infusion syndrome are adverse effects of propofol but it is not clear if they are only dose-dependent or if genetic factors affecting propofol disposition and effects play a role (Tramer et al. 1997; Corbett et al. 2008). A study of genetic determinants of variability in propofol effects in 150 patients found that the time to loss of verbal contact and to a Bispectral Index <70, varied 6.6 and 4.3 fold. There was 15.5 to 111-fold variability in time to emergence, and clearance of propofol varied greatly. There was no statistically significant associations between *CYP2B6* variants (R487C, K262R and Q172 variants), and *GABRE* variants (mRNA358G/T, 20118C/T, 20326C/T and 20502A/T) and the observed inter-patient variability in response (Iohom et al. 2007). SNP's of *UGT1A9* have been found to affect glucuronidation: 2152C > T, −440C > T, −331 T > C, −275 T > A and 98 T > C (Girard et al. 2004). A transversion of 766G > A in the *UGT1A9* gene resulting in the substitution of amino acid D256N was found to increase the risk of suffering adverse effects of propofol (Takahashi et al. 2008). To date, there is no conclusive evidence of PG variations affecting clinical outcomes with propofol anesthesia.

Benzodiazepines

Midazolam is a benzodiazepine whose primary effects arise from reversible interactions with the inhibitor GABA receptor in the CNS. In the liver, CYP3A4/CYP3A5 enzymes metabolize Midazolam to its hydroxyl-derivatives. In compared to wild-type alleles, enzyme induction was about 50% greater in *CYP3A5*3* homozygotes (Floyd et al. 2003). There is significant linkage disequilibrium between *CYP3A5**3 and *CYP3A4**1A in Caucasians, and between *CYP3A5**1 and *CYP3A4**1B in African Americans but did not find any differences in midazolam disposition in vivo between the different genotypes (Kharasch et al. 2007; Miao et al. 2009).

Diazepam is a commonly used benzodiazepine for alleviating anxiety and treatment of muscle spasms. *CYP2C19* enzyme metabolize Diazepam to desmethyldiazepam, and acts by binding to a specific subunit on the GABAA receptor (Oelschlager 1989; Sieghart 1994). The effects of *CYP2C19* polymorphisms were assessed in a study: no variants, *1/*1 (EM; 1 variant, *1/*2 or *1/*3 (IM); and 2 variants, *2/*2, *2/*3 or *3/*3 (PM) in Japanese patients and found that the genotypes affected diazepam pharmacokinetics and emergence from general anesthesia (Inomata et al. 2005).

The presence of a SNP (G681A) of the *CYP2C19* gene in Chinese patients resulted in impaired metabolism of diazepam which is gene-dosage dependent (Qin et al. 1999). These differences in diazepam sensitivity among individuals could be due to variation in the human *GABAA* receptor alpha 4 subunit which has unique

diazepam insensitive binding site (Yang et al. 1995). Another possible reason is Pro385Ser (1236C > T) amino acid substitution in the human GABAA alpha 6 (Iwata et al. 1999).

Etomidate is an intravenous induction anesthetic. It is metabolized by ester hydrolysis. Etomidate acts at GABAA receptors containing 2 or 3, but not 1 subunits. *GABAA* mutation at 2 N265 in Xenopus oocytes and HEK293 cells altered etomidate efficacy while preserving basal and agonist-dependent activity (Desai et al. 2009). Further studies are needed to analyze whether inter-individual variability in etomidate pharmacokinetics is linked to adverse effects such as adrenal insufficiency (Restrepo et al. 2009).

Nitrous Oxide

Although there is negative connotations to the use of nitrous oxide, it is used in clinical practice (Leslie et al. 2011). Nitrous oxide oxidizes the cobalt atom of Vitamin B12 and inhibits the activity of the cobalt-dependent enzyme methionine synthase. Methionine synthase enzyme catalyzes the formation of methionine. The activated form of methionine, S-adenosylmethionine, has a principal role in the formation of the myelin sheath, neurotransmitters and DNA. In an infant boy after exposure to nitrous oxide an unexpected neurological deterioration was reported (Selzer et al. 2003). Post-mortem analysis showed a combination of mutations in 5,10-methylenetetrahydrofolate reductase gene including C677T and A1298C SNPs. These mutations cause 5,10-methylenetetrahydrofolate reductase deficiency in fibroblasts of this infant. This intensified the effect of nitrous oxide on the nervous system and led to the death of the patient. Therefore, in children with these genetic variants there is warning about the possible deleterious effect of nitrous oxide (Erbe and Salis 2003).

Inhalational Anesthetics are metabolized by CYP450 enzymes in the liver (Kharasch and Thummel 1993). Biotransformation of 20–50% of halothane, 2% of sevoflurane, less than 1% of isoflurane and 0.1% of Desflurane are accomplished in the liver (Kharasch et al. 1999). metabolism of inhalational agents except Sevoflurane produces trifluoroacetic acid (Koblin 1992) while metabolism of Sevoflurane produces hexafluoroisopropanol and fluoride (Kharasch 1995). Hepatotoxicity of Halothane has frequently been reported (Kharasch et al. 1996). In rare cases, the effects of liver toxicity of Desflurane, sevoflurane and isoflurane have also been reported (Carrigan and Straughen 1987; Tung et al. 2005; Turillazzi et al. 2007). GABA-ergic mechanisms are responsible for effects of Inhalation anesthetics. In the pediatric population, a postoperative problem is emergence agitation. A Korean study has reported the increased emergence agitation in children with the AA genotype in the GABR2 nucleotide position 3145 in intron A/G. Melanocortin-1receptor (MC1R) mutations in mice affect anesthetic requirement (Xing et al. 2004). In human expression of *MC1R* on the surface of melanocytes affects the melanin biosynthetic pathway and pigment formation. Red hair, which is, linked to increased

Desflurane anesthetic requirements that can be related to particular mutations of the *MC1R* gene (Liem et al. 2004).

Muscle Relaxants

One of the first evidence of pharmacogenetic effect in anesthesia was prolonged apnea after succinylcholine (Kalow and Genest 1957). Prolonged apnea is **due** to variations in pseudocholinesterase activity. Variations in *BChE* gene, another name for pseudocholinesterase, and enzyme result in prolonged neuromuscular blocking effects of succinylcholine and **mivacurium**. Among described variants of the *BChE* gene, the A variant (209A > G, Asp70Gly) and the K variant (1615G > A, Ala539Thr) are the most common variants (Lando et al. 2003). In Caucasian population, the frequency of the heterozygous A-variant and homozygosity is up to 4% and 3 in 1000, respectively. In some ethnicities such as the Jews in Iraq and Iran, the frequency of homozygous A-variant is 1 in 175 individuals and *BChE* activity is reduced by 70% (Vahdati-Mashhadian et al. 2004). For the K-variant, the frequency of heterozygosity varies between 12 to 27% and the incidence of homozygosity is 1 in 63 individuals. It results in 30% reduction of *BChE* activity compared to normal variant. The K-variant was found in 89–96% of individuals with the A-variant, suggesting the linkage disequilibrium of these mutant alleles (Levano et al. 2008). The other mutations are rare, including two fluoride- resistant alleles (F1, Thr243Met and F2, gly390Val), H-variant (Val142Met), J-variant (Glu497Val), and many silent alleles (Nogueira et al. 1992). Biochemical analysis can be used to identify the phenotype (the *BChE* activity) by dibucaine number or fluoride number (Kalow and Genest 1957; Harris and Whittaker 1961). Duration of apnea after 1.0 to 1.5 mg of succinylcholine increases from 5–10 min in homozygous normal to 10–20, 20–35 and 35–60 min in heterozygous one abnormal gene, heterozygous two abnormal gene and homozygous abnormal gene accordingly (Jensen and Viby-Mogensen 1995). Mivacurium is a short acting non-depolarizing muscle relaxant. Rate of Mivacurium hydrolysis by BChE is 70–90% of succinylcholine (Chung and Hardman 2002). Spontaneous recovery from the recommended intubating dose (0.2 mg/kg) is increased from 25–30 min in normal population to 300 min in homozygous atypical genotypes (Lejus et al. 1998).

Pharmacogenomics as Applied to Perioperative Medicine

Perioperative drugs and anesthesia related conditions can be determine based on the data obtained from the genetic sequences and variants. Malignant Hyperthermia (MH) is an autosomal dominant condition. In this condition, abnormal calcium homeostasis causes hypermetabolism, hypoxia, hypercapnia and hyperthermia. It is suggested that one possible reason is mutations in the ryanodine receptor gene

(RYR1) in 70% of cases and mutations in the CACNA1S gene are in 1% of the population. Volatile anesthetics or suxamethonium trigger MH; so for this reason dantrolene (a skeletal muscle relaxant which inhibits calcium release from the sarcoplasmic reticulum) is now kept in theatres and recovery areas. In All patients suspected of having experienced MH, a muscle biopsy is recommended to test contracture condition. In this test, contraction is a positive result. Patients with positive or equivocal results should receive MH-safe anesthesia e.g. total intravenous anesthesia (TIVA). Effective testing decreases the MH mortality rate (Kim 2012).

Propofol infusion syndrome (PRIS) is another example, which can be a target for pharmacogenomic research. PRIS characterizes by metabolic acidosis, rhabdomyolysis, and arrhythmia. Administration of propofol for long time (>48 h) and at high doses (>4 mg/kg/h) results in Arrhythmia. Karakitsos et al. have suggested a genetic basis for this condition. To understand the precise etiology genotyping is essential in patients who have experienced PRIS. This screening based on pharmacogenomic data could be effective in reducing of PRIS incidence. The genetic profiles of individual allow determining a treatment regimen for them based on pharmacokinetic genotype. This strategy could improve the therapeutic efficacy and decrease drug toxicity. For example, monitoring of toxicity is essential in poor CYP metabolizers or if it is appropriate, they should receive *non-opioid based* anesthesia. In patients with opioid receptor polymorphisms, personal capacity for drug metabolism determines the accurate drug dosages that they should receive. This could decrease perioperative morbidity and mortality.

Epigenetics is the study of all types of *gene expression modifications*; both hereditary and acquired ones; while there is no modification in the basic DNA sequence. First coined by Conrad Hal Waddington in 1957, epigenetics is the study of "*non-sequence altering regulatory modifications*" (Naguib et al. 2012; Baedke 2013a). Epigenetic has a highly dynamic pattern (Figs. 2.1, 2.2 and 2.3) and is involved essentially in both normal fate of cell development and human biology and also, a large number of human disease states: while the underlying sequence of DNA is not changed at all in every cell of a human body (except when single mutations occur), each of the multimillion cells of the body have their specific epigenetic pattern which has been developed during the fetal development stages and thrived throughout the lifelong period due to the biologic, environmental, etc. stressors; these epigenetic modifications are not limited to a specific time interval; instead, epigenetic modifications are highly dynamic with a different pattern in each cell, epigenetic changes are not fixed throughout the life span; even the offspring could be affected by epigenetic modifications of their ancestor (Naguib et al. 2012; Lirk et al. 2015; Odell 2018; Crimi et al. 2019).

A number of spatiotemporal factors (including but not limited to environment, diet, exercise, ageing, lifelong disease profile, time factors, different tissue milieu, stressors and toxic agents, drug abuse) affect the process of epigenomics; one of the most important specifications of epigenetics is the inheritability property of the newly appeared patterns which means the effects of stressors may be seen many years later in the next offspring decades later; meanwhile, one should consider the term epigenomics as the combination of "epigenetic mechanisms" and "the results

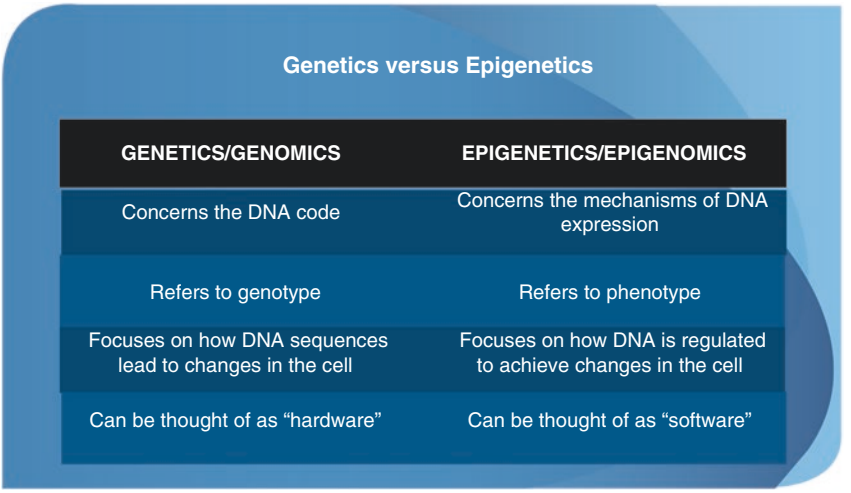

Fig. 2.1 Genetics vs. Epigenetics

Fig. 2.2 Applications of epigenetics in anesthesiology and perioperative medicine

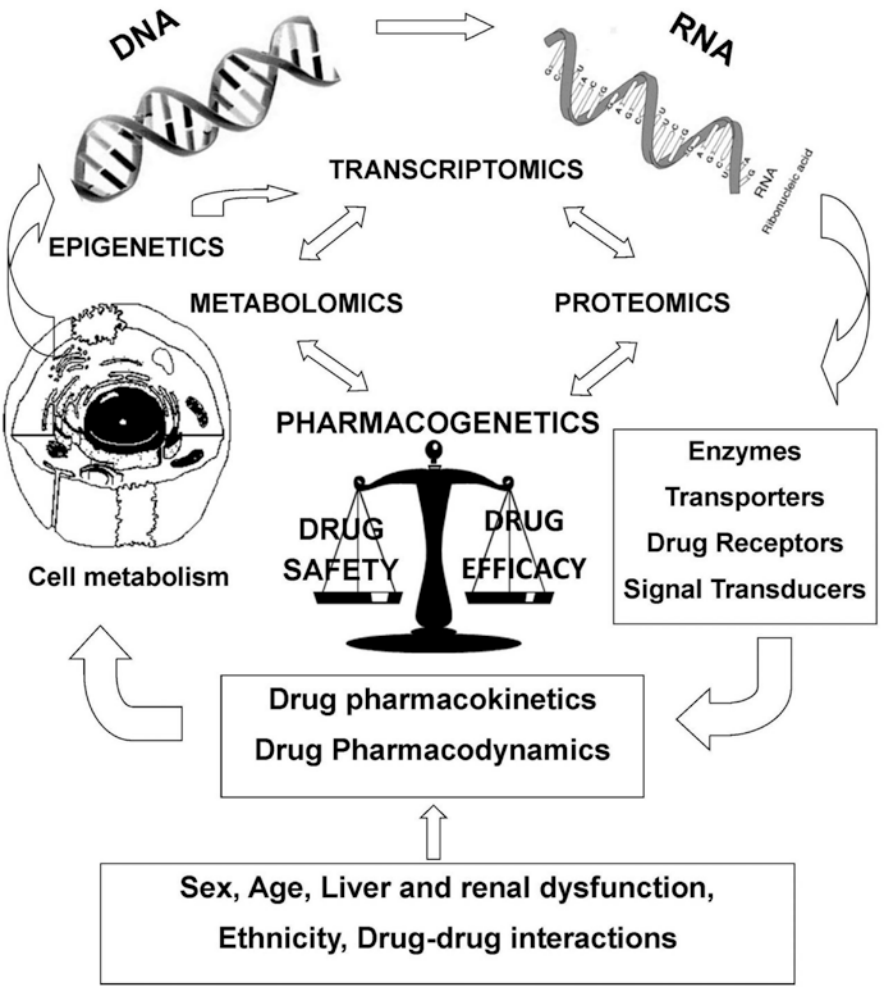

Fig. 2.3 Factors affecting anesthetic safety-efficacy balance

of gene expression" in different cells, tissues and organs (Venter et al. 2001; Bird 2007; Naguib et al. 2012; Lirk et al. 2015; Odell 2018; Zhu et al. 2018; Cavalli and Heard 2019; Crimi et al. 2019).

Epigenetic interactions are responsible for the process of gene expression and phenotype changes due to environmental stressors without any change in DNA sequence. One should remind the great bulk of stresses imposed to patients during the perioperative period, including stressors like drugs, endotoxins and exotoxins, pathologic states, and even the anesthetic drugs basically designed to ameliorate the load of perioperative stress; however, all of them might be a major stressor with the potential to provoke unwanted epigenetic modifications; this is why epigenetics not only affects patient outcome but also by turn, is affected during the perioperative

period (Naguib et al. 2012; Lirk et al. 2015; Degos and Flood 2016; Dirven et al. 2017; Odell 2018).

Among underlying epigenetic mechanisms, the following three titles are the most important ones:

- DNA methylation
- Histone modification (including both acetylation and deacetylation)
- MicroRNAs

Each of the above fields of epigenetics have applications in perioperative medicine which are the research topics in epigenetics studies; meanwhile, there are a number of very important and highly determining "cross-talk" interactions between the above mechanisms of epigenetics; determining the ultimate results of epigenetic interactions in health and disease (Lirk et al. 2015). Moreover, epigenetics remains a very promising perspective for diagnostic and treatment goals for patients undergoing anesthesia during the perioperative period (Naguib et al. 2012; Odell 2018; Crimi et al. 2019).

There are a few main challenges that should be addressed before we could incorporate epigenomics as a daily "routine" in our clinical practice among which these are to be addressed first (Crimi et al. 2019):

- the need to expand current basic and practical knowledge about epigenomics
- the need to expand the daily clinical and point of care technology to use epigenomics
- the challenge of inter-individual variability regarding epigenomics
- the shortage of novel clinically proven drugs

Here, a brief discussion of the three main domains of epigenetics is presented first, afterwards, a few examples of their potential applications in anesthesiology and perioperative medicine is mentioned. However, the interested reader may refer to the studies cited in this chapter, other chapters throughout the book or other more sophisticated texts which are beyond the scope of this book.

Histone Chaperones Inside the nucleosome, there is an innate and natural order regarding integrity, assembly and function of chromatin; which has an essential role in cell biology; however, there are other cellular segments that not only govern the chromatin structure and function, but also, have surveillance over the delicate integrity of the genome-epigenome, enhance DNA stabilization and control DNA unfolding/refolding process and surveillance over the protein processing machinery leading to protein homeostasis (proteostasis). A major contributor to this quality controlling system is called histone chaperones. Chaperone-chaperone and chaperone-cochaperone interactions create an strict, direct and highly ordered network exerting its super controlling function, through mechanisms including but not limited to the following (Ellis 2006; Hartl et al. 2011; Hammond et al. 2017).

- chromatin assembly
- histone provision

- histone recycling
- histone turnover

DNA Methylation Simply discussing, when methyl groups are added to some of the bases in the DNA molecule. DNA methylation does not change the DNA sequence while DNA activity is highly affected. However, this simplistic definition is not all the story. In fact, gene transcription and the following genetic cascade is put down due to DNA methylation. Epigenetically speaking, methyl groups are added to the cytosine end (C) of the two adjacent cytosine-guanine bases located inside the same strand of DNA molecule. The two bases (i.e. cytosine-guanine) are interspersed by a phosphate molecule leading to the combination known as 5′-cytosine-phosphate-guanine-3′ (i.e. 5′-C-p-G-3′). This combination of 2 bases and a phosphate molecule is shortened as CpG. This specific sequence (i.e. CpG) is most frequent in the upstream parts of the gene; here CpG's are collected together to form a "CpG condensed area of gene" known as *CpG island*, abbreviated as *CGI* (Goldman 2001; Venter et al. 2001; Saxonov et al. 2006). Often, CpG islands are located in the promoter part of the gene; having the following items as CpG islands' characteristics (Gardiner-Garden and Frommer 1987; Naguib et al. 2012; Li et al. 2018; Zhou et al. 2019):

- at least 200 base pairs in the DNA region
- a G + C percentage of bases>50% of the base content
- an observed to expected frequency of CpG should be at least 0.6

DNA methylation is handled by an enzyme family known as DNA methyltransferases (DNMT's); in mammalian cells, three main members of this family have been recognized: DNMT1, DNMT3a and DNMT3b with somewhat different functions regarding DNA methylation (Crimi et al. 2019). DNA methylation-related mechanisms are involved in a number of anesthesia related issues to be discussed.

Histone Modification (Including Both Acetylation and Deacetylation) Histones are "protein balls" around which DNA strands have been wrapped. A nucleosome is the basic chromatin unit, including 140 DNA base pairs plus a histone octamer; i.e. each eight histone molecules are packed together to produce a nucleosome core for DNA wrap. The main 5 types of histone molecules found in chromatin are H1/H5, H2a, H2b, H3, and H4; known as "*core histones*". Histone acetylation is the process of acetylating lysine amino acids located on histones which leads to chromatin relaxation; as a result, the process of DNA transcription and gene expression is promoted by histone acetylation. Histone acetylation is mediated by histone acetyl transferases (HATS). On the other hand, if acetyl groups are removed from the histones, the process of histone deacetylation occurs; so, when histones are deacetylated, chromatin compaction occurs and the process of DNA transcription is suppressed, leading to dene silencing; the process of histone deacetylation is mediated through histone deacetylases (HDCAs) which are a group of enzymes; there is a delicate balance between HAT and HDCA leading to a very rapid and highly dynamic control over transcription and gene expression

(Naguib et al. 2012; Jia et al. 2016; Ju et al. 2016; Sakharkar et al. 2016; Wang et al. 2018; Crimi et al. 2019).

MicroRNA MicroRNA or often called miRNA is one of the several types of RNA. They are discussed here as one of the different parts of epigenetics.

Coding and Non-Coding RNA Transcriptomes include coding and non-coding mRNA

- protein coding RNA: Messenger RNA (mRNA) which plays the major role of translating genomes to functioning proteins and were discussed under "transcriptomics"
- non-coding RNA (ncRNA); i.e. tRNA (transfer RNAs), rRNA (ribosomal RNAs), lncRNA (Long non-coding RNAs), small RNA like miRNA (microRNAs), etc.

All types of RNA are not translated to proteins; in fact, only about 1.2% of the human genome is coded to protein; the remaining genome remains noncoding (Jarroux et al. 2017). *Non-coding RNAs* play a major regulatory role in genomics, transcriptomics and epigenetics while do not lead to protein production at all, so they are called "non-coding RNA". However, ncRNAs are functional and play their main role in the expression of genes both in transcriptional and post-transcriptional phases. Main subtypes of ncRNA are lncRNA (long noncoding RNA), miRNA (microRNA), siRNA (Small interfering RNA) and piRNA (Piwi-interacting RNA). These types of noncoding RNA are described here in brief with their potential practical application in anesthesiology and perioperative medicine.

Long noncoding RNA: a group of RNA with more than 200 nucleotides.

MicroRNA: these are small single strand noncoding RNA. Their footprint could be seen in nearly every biologic process of the human body like "proliferation, differentiation, metabolism, hemostasis, apoptosis, and inflammation" (Neudecker et al. 2016; Herkenhoff et al. 2018; Rajaei et al. 2019). A number of different factors like environmental circumstances and/or some stimuli, such as inflammation, hypoxia, or treatment with drugs could affect the expression of miRNA; this is why miRNAs are considered as a promising ingredient in anesthesia and perioperative medicine as "clinical biomarkers & therapeutic measures"; meaning diagnosis and treatment of diseases, and as a novel target for creating new treatments. In this list of treatment novelties, one could look for topics like treatment of acute and chronic pain through different transcriptomic mechanisms in peripheral and central nervous systems, diagnosis and treatment of sepsis and acute lung injury, organ protection during perioperative events, cardioprotection and treatment of ischemic heart diseases and heart failure. Some examples are currently real, like successful treatment of hepatitis C viral infection using anti-miR-122, while others are on the way. Currently, the creation of novel drugs using miRNA approach is through *anti-miRNA molecules* or *miRNA sponges* leading to blockade of natural miRNA and exerting the final therapeutic effect. Besides, molecular mechanisms of anesthetics

action are being elucidated as a basis for future anesthetic drug development through transcriptomic studies (Lutz et al. 2014; Takeuchi et al. 2014; Saugstad 2015; Li and Stary 2016; Neudecker et al. 2016; Bell et al. 2017; Oyama et al. 2017; Saddic et al. 2017; Birklein et al. 2018; Dai et al. 2018; Kreth et al. 2018; Odell 2018).

- siRNA (Small interfering RNA)
- piRNA (Piwi-interacting RNA): these are small RNA with 21–35 nucleotides; almost only in non-human cells

Application of Epigenetics in Anesthesiology and Perioperative Medicine Epigenetics has been proposed as the epicenter of research in anesthesiology and perioperative medicine (Fig. 2.2). The epigenetic landscape developed by Waddington reflects that human diversity is likely the result of a myriad of complex interactions, both intracellular and environmental, rather than a simple one-to-one protein coding of the genome (Baedke 2013b). Knowledge is lacking about anesthetic-induced epigenomic effects. Also, not understood is how the epigenome affects the ways in which an anesthetic agent acts. Epigenetics/Epigenomics in anesthesiology is an important avenue of learning to pursue because humans and other animals have an epigenome. It is likely that at some point, anesthetic intervention outcomes will be influenced by epigenomic changes caused by environmental factors (Skipper 2011; Cortessis 2012). Csoka and Szyf propose that epigenetic side effects of pharmaceuticals are involved in the etiology of heart disease, cancer, neurocognitive disorders, obesity, diabetes, infertility, and sexual dysfunction (Csoka and Szyf 2009).

There exists a knowledge gap in how closely linked anesthesiology and epigenetics are to one another. Although much has been written about anesthesiology, there remain many unknown mechanisms of action and effects of anesthetic medications, which epigenetics could provide scientific explanations for in the future (Biel et al. 2005; Bain and Shaw 2012). Furthermore, the scientific community's burgeoning inquiry into epigenetics fuels continued interest and discourse on this research topic. The chart below provides a simplified comparison of genetics versus epigenetics (Egger et al. 2004; Feinberg 2008; Naguib et al. 2012; Lirk et al. 2015).

Are anesthesia providers knowledgeable about fundamental concepts and seminal research findings relevant to epigenetics in anesthesiology? Considering theory, research, education, and practical applications? Coined by Bilanicz in 2015, "Anesthetic Epigenetics"SM is a novel area of science defined by the study of the interplay between epigenetics, situational circumstances, and the medications administered during the perianesthetic/perioperative care. Anesthesia providers, including Certified Registered Nurse Anesthetists/Anesthesiologists (CRNAs), Student Registered Nurse Anesthetists (SRNAs), Physician Anesthesiologists, Anesthesiology Residents, and Anesthesiology Assistants (AAs), often know little about the interplay between epigenetics and anesthetic medications as identified (Bilanicz 2015).

There are a few teaching program/module available in the literature on the topic to date. However, it is important that anesthesia providers continue to expand their

knowledge on epigenetics and epigenomics in order to optimize patient safety and improve patient outcomes by preventing iatrogenic anesthetic outcomes caused by epigenetic changes (Ferguson-Smith 2011). Moreover, considering epigenetics is critical to the advancement of the anesthesia profession as a whole. Equipped with a greater understanding of how the epigenome and anesthetic agents interact may one day lead to more customized anesthetic delivery to each individual patient (Lirk et al. 2015; Guo et al. 2017).

"Developing Brain" Concerns and Reprogramming of Infant Brain after General Anesthesia General anesthesia (GA) "is intended to bring about five distinct states during surgery: analgesia, amnesia, loss of consciousness, motionlessness, and weakening of autonomic responses" (Surgeryencyclopedia.com 2014). Culley et al. noted that around the year 2000, scientists began to question the return of the brain's functionality after having undergone general anesthesia. This concern is particularly poignant in the infant brain, which when exposed to GA experienced apoptotic neurodegeneration, loss of neural synapses, and cognitive/behavioral deficits moving into maturity as seen in animal models. Synaptogenesis in humans is believed to occur between late gestation and 3–4 years of age, so extrapolating from animal studies and applying to humans, developmental deficits in cognition and behavior may be an inadvertent result of undergoing GA. They also noted that there is a greater than twofold increase in the incidence of Attention Deficit Hyperactivity Disorder (ADHD) in young adults (<19 years old), who underwent two or more GA's before the age of 2 years old. There is some discrepancy in findings as they are not consistently reported between studies and male infants over-represent the infants undergoing GA. Furthermore, it is possible that the surgical stress itself with release of cytokines and other pro-inflammatory mediators may be responsible for the decrease in neurotrophic factors, neurogenesis, and formation of synapses; an example of epigenetic dysregulation. This then, lends credence to the use of anti-inflammatory medications such as non-steroidal to prevent negative effects on neurological dysfunction. So, the consideration of seemingly less offensive anesthetics such as alpha-2 adrenergic agonists (dexmedetomidine) and xenon also warrants investigation (Culley et al. 2012). Csoka and Szyf corroborate that GA agents must further be studied for their effects on return to normal cognition (Csoka and Szyf 2009).

However, aberrancy in DNA methylation (including but not limited to hypermethylation patterns in hippocampal related genes) has been reported following both inhalational and/or intravenous anesthetic exposure in developing animal studies (Ju et al. 2016). Anesthetic exposure is a major concern in fetal development during the last pregnancy trimester and in neonates, infants and children at least up to age 3; based on FDA statement released on December 2016, "repeated or lengthy use of general anesthetic and sedation (i.e. multiple exposures) in children younger than 3 years or in third trimester pregnant women may affect the development of children's brains" (Andropoulos and Greene 2017; Andropoulos 2018; Davidson and Sun 2018).

BDNF (Brain-derived neurotrophic factor) is an important protein present in a number of organ systems including CNS as a mediator of higher brain functions (e.g. learning and memory). BDNF expression has been suggested to be regulated through methylation of its promoter; i.e. epigenetic control. In fact, BDNF is a nerve growth factor with an essential role in development of neural circuits, brain connectivity and neural plasticity properties. Reelin is an extracellular matrix glycoprotein with regulating role on neural processes of the developing brain (Dillon et al. 2017; Badihian et al. 2019; Deyama and Duman 2019; Douma and de Kloet 2019; Zarei-Kheirabadi et al. 2019). Ju et al. demonstrated that sevoflurane exposure in developing rat brain is associated with hypermethylation of hippocampal BDNF and Reelin genes; while pretreatment with 5-aza-2-deoxycytidine (Decitabine) which is mainly a DNMT1 inhibitor prevents these unwanted sevoflurane effects (Ju et al. 2016). Studies similar to the one performed by Ju et al. are promising ones dealing with the use of DNMT inhibitors in preventing aberrant DNA methylation and hence, preventing unwanted effects of anesthetics on neurologic outcomes in developing brain undergoing general anesthesia; so, they may offer personalized novel solutions to deal with one of the most important challenges in anesthetizing neonates, infants and children before age 3 and also, pregnant mothers in their last trimester (Ju et al. 2018; Wu and Zhao 2018; Landin et al. 2019; Walkden et al. 2019).

Pain Management Another major field of study regarding epigenetics and perioperative medicine is the study of pain and pain-related epigenetic interactions; leading to novel diagnostic and therapeutic uses.

There is growing evidence regarding the role of epigenetics in pain management; pain transmission and pain treatment are among the most favorable examples of the role of new treatment methods using transcriptomics; both to discover pain mechanisms and to find out new analgesics (Starobova et al. 2018). However, miRNA studies have found new acute painkillers while the extracellular matrix has been demonstrated to be among the "central molecular pathways in the development of chronic pain" (Parisien et al. 2019). Even more interestingly, neuropathic pain promotes chronic stress and depression through transcriptomic mechanisms (Descalzi et al. 2017). A number of studies in different fields of epigenetics are described here as more tangible examples.

DNA methylation and application of DNA demethylating drugs are incorporated in:

- acute pain
- chronic pain
- cancer pain
- visceral pain
- somatic pain

Regardless of the etiology of pain, increased levels of DNA methyltransferases play an important role in creation, maintenance and control of all types of pain; in addition, increased levels of mu receptor gene methylation has a main impact both

in chronic and/or inflammatory pain and with the same degree of importance, in resistance to opioid analgesics.

DNA methylation, CpG islands and DNMT inhibitors are important topics in many animal and even clinical pain studies, with fruitful promising results (Sun et al. 2015; Shao et al. 2017; Oliveira et al. 2019). Hong, et al., demonstrated the relationship between increased DNA methylation and *"chronic-stress" induced abdominal pain* (Hong et al. 2015). Sun et al. demonstrated that both cancer and acute pain are strongly aggravated by DNA demethylation; in addition, they administered DNMT inhibitors in animal acute pain model and found significant reduction in both thermal sensitivity and allodynia induced by incision (Sun et al. 2015). Meanwhile, some studies have demonstrated the active role of DNMT1 in neuropathic pain genesis; in fact, chronic pain is associated with persistent DNA methylation reprogramming and increased methylation of mu receptor gene leads to opioid resistance against acute pain (Naguib et al. 2012; Zhou et al. 2014; Garriga et al. 2018; Lu et al. 2018; Sun et al. 2019b).

Add to the above, the promising role of DNMT1 inhibitor, i.e. 5-Azacytidine (Vidaza) and 5-aza-2-deoxycytidine (Decitabine) in the treatment of *chronic neuropathic pain*; including its extraordinary pain controlling feature when administered in the rat intrathecal space (Wang et al. 2011). Qi et al. demonstrated that both hydroxylamine and aminooxyacetic acid (inhibitors of cystathionine-β-synthetase) suppressed DRG-induced mechanical hyperalgesia and inflammatory in a dose-dependent manner and demethylation of cystathionine-β-synthetase gene plays an important role in inflammatory pain (Qi et al. 2013). These studies focus on *the role of intrathecal DNA methyltransferase inhibitors* as novel mechanisms especially underlying chronic pain and future windows towards treatment of acute and chronic pain (Sun et al. 2015; Niederberger et al. 2017; Garriga et al. 2018).

Both *histone acetylation* and *histone deacetylation*, known as histone modification, have been involved in development and/or alleviation of pain; mediating different epigenetically mediated pathways; with the resulting dual role of histone modifications in either alleviation or development of neuropathic pain. This is why application of histone acetylation/deacetylation mechanisms in pain management mandates targeted design of isoform- or subtype-specific epigenetic enzymes, if histone modification is used as the mechanism for pain control and developing novel drugs (Liang et al. 2015; Khangura et al. 2017; Niederberger et al. 2017; Aroke et al. 2019).

H4 Histone Acetylation and Pain

Lessans and Dorsey described chromatin remodeling and modification as the key ways that genes express themselves. If this process takes on a pathological shape, then the person will present with an unfavorable health state, such as pain. Identifying pathological shapes and mechanisms may lead to exciting breakthroughs in how pain is treated. Another epigenetic mechanism is methylation of histones, the chief

positively-charged, compacting proteins within the cell's nucleus, to inhibit gene expression or histone acetylation, yielding gene transcription. Histones linked to negatively charged proteins along the DNA backbone form chromatin. The authors note that pain is the most frequent cause for seeking out health care provision and over 350 genes are currently relevant in clinical and experimental pain with countless more involved in analgesia regulation. Yet, the genes themselves are not the only answer in how people experience pain. Transcriptional and translational epigenomic mechanisms guide how one progresses through the pain continuum (Lessans and Dorsey 2013).

As mentioned, one of anesthesia's goals is to provide analgesia. Known pathology involved during the transition from acute to chronic pain can be supplemented by the study of epigenetic mechanisms involved in the nervous system's plasticity. Moving from the periphery to the brain's cortex, nerve or tissue damage leads to pathologic connections developing, leaving some people with chronic pain and dysfunction. Furthermore, life's environmental factors may serve as epigenetic primers for how individuals experience pain and analgesia (Lessans and Dorsey 2013). In the meantime, some consensus exists on neurogenic pain's development being related to NMDAR-mediated plasticity. So, agents like Ketamine, already proven beneficial in treating acute pain, may be helpful in the prevention of chronic pain (Javitt et al. 2011).

Lirk et al. further describe how pain is tied to epigenetic mechanisms. Both opiates and local anesthetics are fundamental parts of perioperative pain management. Opiates seemingly lead to global DNA methylation whereas local anesthetics (LAs), as a class, lead to global DNA demethylation. They explained the work of Hwang et al., who showed that the expression of the mu opioid receptor is mediated by DNA methylation. In P19 embryonic cells, proximal promoter regions for the mu receptor were hypermethylated and gene silencing ensued. But, when exposed to retinoic acid, the mu receptor gene is expressed stably in mature astrocyte/neuronal cells and coincidentally with decreased MeCP2 binding in the promoter region. When methylated DNA is bound by MeCP2, there is histone deacetylation, histone compacting, and decreased transcription of the mu receptor and hence, without appropriate MeCP2 binding there is an overexpression of the mu receptor. (Lirk et al. 2015).

Lirk et al. further described that among the negative effects of opiates are nausea, vomiting, respiratory depression, slowed bowel peristalsis, and opioid-induced hyperalgesia (OIH), an excessive sensitivity to pain (Lirk et al. 2015). Development of OIH varies with the type of opioid used. OIH seems the worst with Remifentanil and least with buprenorphine, a partial mu receptor agonist and K receptor agonist, and is prevented by Ketamine, as described earlier, a NMDA receptor antagonist. In an article by Liang and colleagues, inhibiting histone acetyltransferase when morphine, the model opiate, was present in mice led to less signs of OIH, whereas inhibiting histone deacetylase worsened OIH (Liang et al. 2013).

Lirk and colleagues explained that systemic absorption of LAs after local injection, such as lidocaine and ropivicaine, and the direct intravenous injection of them have been under investigation for both analgesic and anti-inflammatory effects.

Local anesthetics demethylate by at least one identified mechanism, inhibition of DNA methyltransferase. It stands to reason that preventing methylation-induced hyperalgesia, as described above, may be a potential target for the demethylating effects of LAs. Beyond this, the perioperative period is associated with increased inflammatory mediator release, which is regulated by histone methylation. Here, the epigenetic demethylating property of LAs may potentially serve to prevent/treat surgical inflammation (Lirk et al. 2015).

Alvarado et al., hypothesized that changes to promoters and enhancers of genes via DNA methylation lead to alterations in gene expression resulting in brain structure and function because of pain. Synaptotagmin 2 is a membrane-trafficking protein and a regulator of synaptic function. Increased synaptotagmin is present in synaptogenesis reflecting synaptic density and plasticity (Alvarado et al. 2015). Virok et al. showed that increased chronic restraint stress positively correlated with Synaptotagmin 2 expression in the PFC of rats (Virok et al. 2011a, b). This supports the hypothesis of Alvarado and colleagues that chronic anxiety/stress, whatever its source, may result in profound changes in synaptic structure +/− function. The rats, which were subjected to peripheral nerve injury had hypomethylated CpG (5′-Cytosine-phosphate-Guanine-3′) promoter sites for Synaptotagmin 2 expression in their PFC, which coincided with signs of chronic pain 6 months post injury as compared to control rats, which had neither (Alvarado et al. 2015).

Sahbaie and colleagues used mice to test how chronic and escalating morphine doses would lead to OIH and long-standing epigenetic changes after a surgical insult to one hindpaw of each mouse. The mice that received continuous opioids were more tolerant to the analgesic effects of morphine and also experienced greater pain sensitization than the control group. Two proteins, BDNF and Prodynorphin (Pdyn), both present in the spinal cords of test mice were upregulated via acetylation of the promoter region of the opioid exposed mice. When anacardic acid, an acetyltransferase inhibitor, was co-administered with morphine, these mice had less OIH and attenuated enhanced hyperalgesia. To explore other ways to also diminish hyperalgesia, the researchers also trialed the effects of a selective tropomyosin-related kinase B (ANA-12) and K-opioid receptor antagonist (nor-binaltorphimine). Both were administered intrathecally and found to limit hyperalgesia one or three days after surgery (Sahbaie et al. 2009, 2016; Sun et al. 2015).

Resistance to Opioid Analgesics and Opioid Addiction The afterwards of analgesic tolerance (resulting in chronic abuse or overuse of the analgesics) is nowadays a great and challenging dilemma in medicine with huge societal impact; personalized control of pain could be a suitable approach to fix these challenges especially when applying epigenetics-mediated approaches (Benzon and Anderson 2017; Hah et al. 2017; Yaster et al. 2017; Burton et al. 2019).

Ablation of mu opioid receptor (MOR) gene in primary sensory neurons or increased MOR methylation in dorsal root ganglion (DRG) affects pain sensitization after incision, leads to opioid resistance against acute pain and results in chronic opioid tolerance (Naguib et al. 2012; Zhou et al. 2014; Mo et al. 2018; Sun et al. 2019a; Browne et al. 2020).

One of the probable protein families needed for DNA methylation triggered gene transcriptional repression is the Methyl-CpG-binding domain (MBD) family; which includes MBD1–4 (Li et al. 2015); meanwhile, for acute and chronic pain generation, expression of DRG MBD1 is a prerequisite; the underlying mechanism is possibly through modulating expression of Oprm1 (opioid receptor mu 1) and Kcna2 (Potassium voltage-gated channel subfamily A member 2) genes in the DRG neurons; controlled by DNA methyl transferases (Ludwig et al. 2016; Browne et al. 2020). In addition, deficiency in MBD1 leads to increased MOR gene-mediated analgesia in animal model with decreased level of MOR-mediated analgesic tolerance through epigenetic silencing of Oprm1 and Kcna2 Genes in Primary Sensory Neurons (Lu et al. 2018; Mo et al. 2018; Sun et al. 2019b). These studies suggest that epigenetic modifications in MOR gene located in primary sensory neurons would be new strategic treatment for acute and chronic pain while reducing the untoward challenge of opioid tolerance and/or abuse and developing novel plans for treatment of opioid addiction using epigenetic mechanisms (Hurd and O'Brien 2018; Browne et al. 2020).

Impaired DNA methylation (through spinal BDNF and PDYN epigenetic changes) is a key mechanism in development of opioid induced hyperalgesia (OIH); one of the most important pathological mechanism in opioid tolerance development is OIH; opioid tolerance is a great dilemma for anesthesiologists in perioperative acute pain management; epigenetic-mediated blocking of BDNF and prodynorphin (PDYN) propose applied counter-mechanisms to manage OIH and acute pain in the near future (Lirk et al. 2015; Chao et al. 2016; Sahbaie et al. 2016).

Finally, treatment of opioid addiction and/or controlling pain in analgesic resistant patients or even acute pain control in otherwise healthy people is a typical example for application of personalized medicine in anesthesiology and perioperative medicine (Hurd and O'Brien 2018).

Perioperative Brain Protection: Preventing Brain Ischemia and Postoperative Cognitive Disorders (POCD) One of the most important goals in the perioperative period is to perform brain protection; preventing any potential ischemic, metabolic or pharmacologic CNS damage. However, current strategies would not guarantee CNS integrity in all the patients. There is increasing role for epigenetically mediated brain protective strategies. However, these potential approaches are highly personalized in nature.

There are a number of candidates as potential treatments for managing perioperative brain insults; though in human studies there is a considerable challenge in this field; studies do not agree whether POCD is the result of anesthesia/anesthesia methods itself or a result of combined "surgical-anesthesia-patient" factors (Belrose and Noppens 2019).

BDNF a mediator of higher brain functions regulated by epigenetic control mechanisms is an important controller of the CNS, as mentioned above. Volatile anesthetics have been shown to induce POCD in animal models through epigenetic control of BDNF. In a study by Ji et al. isoflurane could suppress BDNF-tyrosine kinase receptor B (TrkB) signaling pathway through suppression of histone

acetylation; moreover, they used sodium butyrate (a histone deacetylase inhibitor) to reverse isoflurane-induced POCD; they concluded this approach could be a promise in management of isoflurane-induced POCD (Ji et al. 2014). In addition, Wu et al. demonstrated similar results regarding isoflurane-induced POCD model in aging mice; they found that isoflurane-induced POCD could be rescued using reversal of mitochondrial dysfunction by SS-31 and finally enhances BDNF-related mitochondrial signaling pathway; SS-31 is the short name for "D-Arg-2′6′-dimethylTyr-Lys-Phe-NH2' which is a mitochondria-related antioxidant (Wu et al. 2016; Dridi et al. 2020).

In animal models, sevoflurane anesthesia was demonstrated to lead to POCD through epigenetic mechanisms including suppressing BDNF expression; the effect of sevoflurane on BDNF is mediated through inhibition of histone acetylation (Yu et al. 2019). On the other hand, 14-3-3ζ mediated increase in BDNF has been demonstrated in animal models as a preventive measure in brain ischemia (Chen and Chen 2017; Hing et al. 2018; Khalesi et al. 2019).

The role of epigenetic aberrancy in a number of diseases like Alzheimer's and Rett syndrome had led us to the application of epigenetics in more sophisticated assessment of POCD and possibly, prevention or treatment of POCD.

POCD is a major challenge; especially in the elderly patients undergoing surgery. In the latter patient group, the association between POCD and global hypomethylation of leukocyte DNA has been demonstrated. In addition, Li et al. found that early development of POCD was in association with postoperative leucocyte DNA hypomethylation. On the other hand, any imbalance in the chaperone system may exert significant unwanted effects on the cognitive function. Wang et al. found that in aged patients with postoperative cognitive dysfunction, there was increased expression of FKBP51, a steroid receptor chaperone, in peripheral blood leucocytes (Zhou et al. 2014; Cortese and Burger 2017; Zhu et al. 2017; Li et al. 2019; Wang et al. 2019; Cui et al. 2020).

During the perioperative period, the patients demonstrate a defensive reaction against the surgical stimuli: the stress response. While this is a protective and defense mechanism, there are untoward afterwards; one of them is the inflammatory response; which is often a short term response. However, pending upon the stress magnitude, the inflammatory response might to high with resulting sequelae; one of them is the neuroinflammatory sequelae, being associated with a range of neurological results including neuronal injury, cognitive disabilities and POCD. There is a key role for glucocorticoid receptors (GR) in maintenance of stress level leading to POCD. However, a number of different factors govern GR expression throughout life including FK506 binding protein 51: "FKBP51". In clinical setting, POCD in the elderly was associated with glucocorticoid resistance and increased FKBP51 expression; interestingly, there is a potential that FKBP51 blockers could be a "future" therapeutic modality to control chronic pain and stress-induced disorders; possibly a new member among the armamentarium for perioperative stress and pain control (Zannas et al. 2016; Wang et al. 2019).

It has been demonstrated that stress provoked during early life, begets "*cognitive dysfunction after sevoflurane anesthesia*". Based on the evidence that demonstrate

modifications in the expression and/or function of the glucocorticoid gene receptor (GR) promoter due to misadventures or mishaps in early life time; this process is mainly mediated through aberrant GR promoter gene methylation, leading to its suppression; the result would be exaggerated neuroinflammatory response seen as cognitive dysfunction after sevoflurane anesthesia in later life years as aftermath of early life mishaps (Zhu et al. 2017). This study and similar ones stress on the role of epigenetically mediated mechanisms in development of POCD; here as a result of early life adversity. The same mechanisms may be responsible for occurrence of cardiovascular and endocrine disorders by epigenetically mediated early life events; which are not only responsible in the same person, but also could possibly be transferred to the next generations; a finding which stresses on the role of appropriate approaches used by anesthesiologists to manage child separation in the operating room entry (Wilkinson et al. 2018; Coley et al. 2019; Vidrascu et al. 2019).

There are a list of different molecules which are potential candidates for POCD treatment and/or prevention; however, most of them are in the preclinical stage. In an animal study the role of DNA 5′-hydroxymethylcytosine (5hmC) modification was demonstrated on the learning and memory defects observed in POCD; however, 5hmC is a cytosine-derived base with significant role in epigenetics; mainly in brain and embryonic stem cells (Kriaucionis and Heintz 2009; Zhong and Xu 2019).

Histone Methylation, DNA Methylation and Long-Term Memory There are a number of ways through which histone methylation may be dysregulated in long-term memory formation and in cognitive impairments like schizophrenia. Possibly both silencing of genes and transcriptional activation, specifically, oppositely focused processes, acting on different histone areas are necessary in consolidating memory. Methyltransferase is an important enzyme in the methylation process (Gupta et al. 2010). Based on these researches, it stands to reason that if a given anesthetic could affect methyltransferase activity or some other yet unknown mechanism, then memory could be negatively impacted.

How epigenetic mechanisms impact long-term memory formation? It seems that histone acetylation and histone deacetylation as controlled by histone acetyltransferase and histone deacetylase (HDAC) activity, respectively. The presence of HDACs, specifically HDAC2, have a negative impact on long term memory formation by muffling key genes in learning and memory such as brain-derived neurotrophic factor (BDNF), calmodulin-dependent protein kinases (CaMKII), and cAMP response element binding protein (CREB). These researches also show cellular apoptosis as a result of exposure to inhaled anesthetic. On the other hand, neuroprotection can occur by using HDAC inhibitors like valproic acid (Jarome and Lubin 2014; Ji et al. 2014).

Chestnut et al. further studied how epigenetic regulation via DNA methyltransferase (Dnmt) is part of motor neuron cell death. Used to inhibit Dnmt catalytic activity, RG108 and procainamide (a sodium channel blocking antiarrhythmic) protected cultured neurons from excessive DNA methylation and apoptosis (programmed cell death). Dnmt-influenced apoptosis is linked to human amyotrophic lateral sclerosis (ALS) (Chestnut et al. 2011). So, if procainamide is taken, the

motor neuron cell may be protected, but what of the drugs that may conversely affect these same cells? And, what inherent individual epigenetic traits does the one undergoing anesthesia bring to the equation?

Hypermethylation of Hippocampal Synaptic Plasticity-Related Genes with Sevoflurane Exposure Sevoflurane is an inhaled anesthetic used to induce GA. A number of researchers studied how neonatal rats exposed to sevoflurane functioned cognitively via the open field test, fear conditioning, and the Morris water maze. Neonatal rats (male only) were separated into five groups: control, control +5-aza-deoxycitidine (5-AZA), sevoflurane, sevoflurane + dimethyl sulphoxide (DMSO, vehicle), and sevoflurane+5-AZA. Experimental rats were exposed to 3% sevoflurane for two hours on three consecutive days and then, euthanized serially at 1 h, 6 h, 24 h, and 30 days after the last sevoflurane exposure. The hippocampus was then dissected, DNA isolated, and the DNA methylation status of the synaptic plasticity genes, Brain-derived neurotrophic factor (BDNF) and Reelin genes, assessed. There was a decreased expression of both BDNF and Reelin due to DNA hypermethylation in the Sevoflurane and Sevoflurane + vehicle groups, which manifested as a decreased number of dendritic spines in the pyramidal neurons of the hippocampus—an indication of decreased synaptic plasticity. Also, found was increased DNA methyltransferases (DNMTs), specifically DNMT 3a and DNMT 3b, and decreased methyl CpG binding protein 2 (MeCP2). This further coincided with decreased cognition on behavioral exams. In those rats, which were injected with 5-aza-2-deoxycytidine (5-AZA), a DNA methyltransferase inhibitor, and in the control group the above changes/manifestations were not seen after sevoflurane exposure and subsequent DNA analysis (Ju et al. 2016).

Isoflurane-Induced Decreases in Histone Acetylation and Cognition Isoflurane is another inhaled anesthetic used for GA induction. Ji et al. studied the effect of isoflurane on rats' cognition and histone acetylation and found both decreased with repeated isoflurane exposure. Also, the hippocampal BDNF-tyrosine kinase receptor B (TrkB) pathway needed for memory consolidation, CREB, CaMKII as well as, downstream signaling, phospho-calmodulin-dependent protein kinase and phospho-cAMP were diminished. Sodium butyrate (NaB), when intraperitoneally injected into study rats, inhibited histone deacetylase (HDAC) and increased neuronal histone acetylation, actively preventing cognitive decline. Repeated exposures to Isoflurane further led to increased hippocampal inflammation, as evidenced by increased levels of interleukin 1*B* (IL-1*B*) and interleukin 6 (IL-6), to cellular apoptosis (programmed cell death), and to diminished cognition on behavioral tests. Again, NaB ameliorated these effects and potentially may serve an important role in future anesthesia practice (Ji et al. 2014).

Cannabis (Endocannabinoid) Effects on Inflammation, Oxidative Stress and Micro RNA (mRNA) Expression The use of cannabis both medicinally and recreationally has increased over recent years and to date 42 out of 50 U.S.A. states have legalized or decriminalized its' use in one way or another. Cannabinoids are

heavily concentrated in the plant *Cannabis sativa*. Over 100 related molecules collectively make up types of C-terpenopenols, which are grouped into delta-8-tetrahydrocannabinol (Δ8-THC), Delta-9-tetrahydrocannabinol (Δ9-THC), cannabidiol (CBD), and cannabicyclol. These are further classified by chemical origin as phytocannabinoids, endocannabinoids (eCBS), and synthetic cannabinoids. The endocannabinoid system is particularly important as it is involved in lipolysis, energy balance, metabolism, cognition, and behavior. In addition, Δ9-THC and CBD are the most deeply researched cannabinoids and act on both the peripheral nervous system (PNS) and the central nervous system (CNS). Human endogenous receptors include cannabinoid receptor 1 (CB1) found primarily in the (CNS), cannabinoid receptor 2 (CB2) found mostly in immune cells modulating immune response showing both pro- and anti-inflammatory processes, and cannabinoid receptor 3 (CB3) in the endothelium and spleen (Wilkinson 2013; Hunt and Pacula 2017; Pacula and Smart 2017; Stoecker et al. 2018; Dinu et al. 2020).

Furthermore, there is reduced systemic inflammatory response and oxidative stress and increased immune modulated neuronal protection through the synergistic effects of Δ9-THC/CBD. Cannabinoids have proven useful in decreasing pain associated with inflammation including neuropathic pain. Some mechanisms include increased antioxidant effects on nerve fibers, decreased IL-6, TNF-α, and iNOS expression, decreased leukocyte migration, and decreased cytokine production on macrophages. The clinical applications of cannabinoids in anesthesia practice are intriguing. These researchers believe that an important epigenetic mechanism at play in the inflammatory cascade is seen in the context of sepsis, which induces the cannabinoid signaling system to express micro ribonucleic acids (microRNAs), non-coding single-stranded RNAs with 19 to 25 nucleotides. Mature microRNA's leave the cell as apoptotic bodies, exosomes, or lipoproteins that are part of intercellular communication pathways. When CB1 or CB2 for example are stimulated by Δ9-THC and CBD in an inflammatory state, the expression of micro RNA-21, microRNA-146, and microRNA-155 is seen limiting downstream inflammatory marker release. T-cell biosynthesis of cytokine and expression of IFN-γ and IFN-α are reduced via Δ9-THC exposure and subsequent microRNA activity; there are similar researches in favor of these findings (Lafreniere and Lehmann 2017; Rogobete et al. 2018; Szilágyi et al. 2019; Dinu et al. 2020).

Ketamine-Induced Unknown Epigenetic Mechanism in Depression Ketamine (a synthetic N-Methyl D-Aspartate aka NMDA) is a medication commonly used to induce general anesthesia and to treat pain. It works on the NMDA receptor (NMDAR) as an antagonist. Usually, glutamate and aspartate, both excitatory neurotransmitters, engage NMDAR, as well as, D-serine (possibly through phosphorylation), which acts as a co-agonist thereby increasing neurotransmitter excitation. NMDAR is involved in cellular membrane depolarization, rapidly increasing permeability to magnesium and calcium, linked to synaptic plasticity of neurons and hence, affecting how organisms learn and memory development. Depression is characterized by pleasure loss, decreased cognition and memory, and alterations in sleeping, eating, ambulation, and sexual behaviors. In depression, there appears to

be atrophy of the neuron, decreased neuron number in the brain's cortex and limbic regions, and slowed neurotransmission across neurons. Commonly used antidepressants such as selective serotonin reuptake inhibitors (SSRI's) are used to flood the synapse with neurotransmitter to aid in neuronal communication and to treat symptoms of depression; however, the effects SSRIs take weeks to months to materialize and often only lead to moderate symptom relief. Here, ketamine shows promise as an effective antidepressant, due to its seemingly rapid synaptogenesis and reversal of the atrophy caused by chronic stress, a known depressive factor, in rodents. Reversal of depressive symptoms via a single dose of ketamine has been seen within as little as a few hours in treatment-resistant patients lasting seven to ten days. Chronic stress leads to decreased brain-derived neurotrophic factor (BDNF), necessary for neuronal development early in life and for the survival and function of neurons in adulthood. Fluoxetine, an SSRI, acts on the BDNF molecule to increase excitatory glutamate activity, but only modestly in comparison to ketamine. In activating BDNF release, ketamine leads to increased signaling and subsequent translation of synaptic proteins such as glutamate A1 (GluA1) and activity-regulated cytoskeleton-association protein (Arc) (Strahl and Allis 2000; Jenuwein and Allis 2001; An 2007; Duman and Aghajanian 2012; Duman et al. 2012; Liu et al. 2012). In this way, we see some evidence of an unknown epigenetic mechanism activated by ketamine turning on a specific physiologic pathway, with potential clinical applications.

Epigenetics and Stress Response Management The effect of different *anesthetic regimens on the stress alleviation* has been demonstrated in animal models (Le et al. 2019). It seems to be plausible to have the same mechanism in human anesthesia; so, it would be possible to use transcriptomics as a method for tailoring individualized anesthetic regimen for each patient based on transcriptomic assessments; including but not limited to adjusting the potency of the anesthetic drugs in stress response modification.

Organ protection is among the potential properties of some anesthetic drugs; for example, the role of volatile anesthetics in ischemic preconditioning has been studied with different results based on the anesthetic volatile gas, the dose of the gas, the target organ and remote or direct ischemic effect; though a preserving in renal tubules role has been shown for Isoflurane through TGF-β1-dependent effects of Isoflurane, leading to generation of CD73 (ecto-5′-nucleotidase) and adenosine in renal tubules (Kim et al. 2013). Besides volatile anesthetics, Heydarpour et al. demonstrated the protective role of lidocaine on myocardial tissue when added to cardioplegia in patients undergoing cardiac surgery with cardiopulmonary bypass using "whole-genome RNA sequencing of the human left ventricular (LV) myocardium" (Heydarpour et al. 2018).

Ischemic heart disease is one of the challenges in the perioperative medicine especially during intraoperative and postoperative stress provoking events. Muehlschlegel et al. demonstrated remarkable changes in the gene expression of human left ventricle when receiving cold cardioplegia during cardiac surgery with

cardiopulmonary bypass (Muehlschlegel et al. 2015). Saddic et al. assessed the role of long noncoding RNAs (lncRNAs) from myocardial tissue of patients undergoing cardiac surgery and proposed lncRNAs as potential diagnostic and therapeutic targets for ischemic heart disease (Saddic et al. 2017) which could be potentially applicable in perioperative ischemic cardiac events. In addition, loss of RNA expression and altered allele-specific transcriptional expression is associated with congenital heart diseases; which could be a helpful diagnostic tool for these patients (McKean et al. 2016). These studies and other similar ones have opened new horizons in the diagnosis and management of cardiac diseases and in a wider spectrum, these are new approaches in personalized medicine aiming perioperative clinical management of different organs especially in our daily clinical practice (Koeppen et al. 2015).

MicroRNA-21-Mediated Cardioprotective Effect of Isoflurane Gas The potential mechanisms by which isoflurane induces cardioprotection in mice have been studied in a number of animal researches. Isoflurane is another inhaled anesthetic used for GA induction. Microribonucleases (RNAs) are single stranded, noncoding, endogenous molecules approximately 22 nucleotides long and key regulators of gene expression. Micro RNA-21 is inherent to cardiomyocytes, the vascular endothelium, vascular smooth muscle cells, and cardiac fibroblasts. The current evidence points towards the role of micro RNA-21 in cardiac cell and vascular smooth muscle cell proliferation and apoptosis, as well as, in the functionality of cardiac fibroblasts. Pathophysiological events like myocardial infarction (MI) and congestive heart failure are being investigated with linkages to micro RNA-21 and have found that treatment with isoflurane protects mice from ischemia/reperfusion injury by a microRNA-dependent mechanism; while protein kinase B/nitric oxide/mitochondrial permeability transition pore (Akt/NOS/mPTP) pathway is in involved in this phenomenon. Isoflurane is cardioprotective because it upregulates micro RNA-21 expression, downregulates the expression of RHOA (micro RNA-21 target), and lessens MI size and improves recovery of cardiac cells after ischemia/reperfusion by delaying mPTP opening, slowing cell death, and increasing phosphorylation of Akt and NOS in the ischemic/reperfused myocardium (Qiao et al. 2015; Stary et al. 2015; Das et al. 2018; Caccioppo et al. 2019; Dehaini et al. 2019; Pant et al. 2019; Yoshikawa et al. 2019; Kura et al. 2020).

Sevoflurane-Induced Down-Regulation of Hippocampal Oxytocin and Arginine Vasopressin Zhou et al. exposed neonatal, 20 day old mice to either air or sevoflurane gas for 6 h. After mice were exposed to their respective gases, they were introduced to the same stimulus mouse for five minutes with a thirty-minute break for a total of four sessions. The length of time spent smelling within two centimeters of the introduced mouse was recorded. At the fifth session, the same stimulus mouse and a novel mouse were introduced. The sevoflurane-exposed mice took longer at each introduction to become familiar with the stimulus mouse and then, at the fifth session, to discriminate between the mice they already were familiar with and the novel one, showing a slowed learning response. Mice were then euthanized and the

hippocampus of each was resected. The amount of oxytocin and arginine vasopressin was markedly different between groups, where the sevoflurane group had less of both hormones present and down-regulation of their respective messenger RNA (mRNA). Based upon previous related research and their own findings, Zhou et al. question whether methylation of the oxytocin and arginine vasopressin gene promoters leads to down-regulation of their transcription (Liang et al. 2010; Zhou et al. 2015a, b; Ben-Ari 2018; Marquardt et al. 2018).

MTHFR 677T Polymorphism, Homocysteine Elevation and Nitrous Oxide-Related Myelopathy The enzyme 5,10 methylenetetrahydrofolate reductase (MTHRF) is the catalyst that reduces 5,10 methylenetetrahydrofolate to 5-methyltetrahydrofolatem, the predominant type of circulating folate and donor of carbon for remethylation of homocysteine to methionine. Methionine is methylated throughout biochemistry and important in many ways including myelin sheath formation and in DNA synthesis. Nitrous oxide (N_2O), a volatile gas used in general anesthesia, oxidizes the cobalt atom of vitamin B12 irreversibly, which inhibits the cobalamin-dependent enzyme methionine synthase. Hence, N_2O leads to decreased MTHRF activity. In addition, the autosomal recessive inheritance of the thermolabile form of MTHRF, a genetic mutation resulting from a 677 cytosine to thymine altered pairing such that valine instead of alanine is expressed. The thermolabile MTHRF is associated with elevated plasma homocysteine levels (hyperhomocysteinaemia) and decreased MTHRF activity. Coronary artery disease, neurological deficit, neural tube defects have been investigated as linked to low MTHRF activity. There has been a patients exposed to N20 serially for surgical repair of cervical spinal stenosis had been presented with increasingly severe neurological deficit up to and including paralysis, possibly due to decreased MTHFR activity because of the irreversible oxidation of the cobalt atom of vitamin B12 (folate) from N20 administration, an inherited MTHFR gene mutation, and hyperhomocysteinaemia. The patient's neurological dysfunction has been slowly restored using folic acid and vitamin B12 supplementation. Although the genetic screening for MTHRF mutation is not routinely practiced, it may be perhaps influential in the practice of anesthesia in upcoming years, particularly in context of N_2O administration. However, a specific epigenetic mechanism has not been definitively assigned to the latter mechanisms, though there is one (or more) in play because the mutated MTHFR is expressed phenotypically (Selzer et al. 2003; Lacassie et al. 2006; Shay et al. 2007; Nagele et al. 2013; Chi 2018).

Carcinogenicity of Anesthetics It has been proposed that pharmaceutical agents have carcinogenic effects both by genotoxic and epigenetic mechanisms. Hydralazine, a vasodilating antihypertensive agent, is oftentimes used perioperatively to control increased blood pressure. It has been found to have direct genotoxic effects (damage to DNA structure itself) in rabbit hepatocytes, the rabbits were slow acetylators. Humans, like rabbits, are polymorphic in their activity of N-acetyltransferase (NAT), a key enzyme in the metabolism of hydralazine. Unknown at the time was the potential role of epigenetic mechanisms. Hydralazine

inhibits DNA methylation with the potential of triggering a lupus-like autoimmune response. This reaction may be related to the body's global genomic hypomethylation yielding an under-expression of proteins, and hence, recognition of a non-self/foreign body state. Thalidomide a sedative-hypnotic is no longer in use as an anesthetic, due to its now known teratogenic effects. Yet, it remains in use as a chemotherapeutic agent. Historically, fetuses exposed to thalidomide from the 21st through the 40th days of gestation often died of bowel atresia, kidney or heart malformations. These thalidomide-exposed fetuses, once born, often had truncated upper limbs and some of those who bore offspring also had offspring with shortened limbs. The fact that it is a heritable trait may point toward epigenetic mechanisms at work such as altered DNA methylation or an alteration of sequence-specific DNA binding proteins. Add to the above the finding that potential role of HDAC inhibitors in the treatment of cancer has been described. Although histone acetylation globally regulates gene expression, HDACs affect a smaller subset of genes associated with cell growth control. HDAC inhibitors are proving effective in stopping leukemia and solid tumor growth (Williams et al. 1980; McQueen et al. 1982; Biel et al. 2005; Keppler and Archer 2008; Csoka and Szyf 2009; Cichewicz 2010; Alvarado et al. 2015; Raftopoulos et al. 2015; Kim and Tae 2016; Berkel and Pandey 2017; Kim et al. 2017; Dhall et al. 2019).

Transcriptomics transcriptome is "the readout of the genome". In other words, it is the study of all RNA types (i.e. all forms of transcripts) in any form; which are collectively the set of all RNA molecules in one cell or a cell population and lead to transcription form DNA molecules; hence, transcriptomics could provide us information about gene expression (Clancy 2008; Blow 2009).

Unlike the genome, which is essentially a static entity, the transcriptome can be modulated by both external and internal factors. The transcriptome thereby serves as a dynamic link between an organism's genome and its physical characteristics.

An increasing bulk of evidence stress on the role of transcriptomes in many "clinical events" of anesthesiology and perioperative medicine. This section includes a brief review on this topic with a look forward to new paths in anesthesiology and perioperative medicine with transcriptomic approach, some of them are current clinical practice (Gingeras 2007; Gerstein et al. 2014; Muehlschlegel et al. 2015; Neudecker et al. 2016; Xia et al. 2017; Kreth et al. 2018; Raithel et al. 2018).

There are a number of different methods for analysis of transcriptomes; however, all techniques involve using transcriptome-based cDNA synthesis (Shendure et al. 2004; Lowe et al. 2017; Starobova et al. 2018).

Serial Analysis of Gene Expression (SAGE) is one of the basic transcriptomic techniques which provides gene expression analytic data with following characteristics (Lal et al. 1999; Saha et al. 2002; Tuteja and Tuteja 2004; Wang 2007):

- rapid
- quantitative
- comprehensive and inclusive
- without the need to have a preexisting clone
- could be used for both known and unknown clones

- identifying normal transcriptomic and genetic pattern
- diagnosing abnormal transcriptomic and genetic pattern changes

SAGE is used for both identified and new clones since it does not necessarily need a prerequisite of a hybridization probe for each transcriptomic study. The technique used in SAGE is through creating snapshots of the transcripts usually in a small study sample; in other words, SAGE produces small tags of mRNA based on the related transcript. These small tags (snapshots) of mRNA are then used to create cDNA fragments; after finalizing the picture taken from the whole transcript, using the power of digital analysis, the pattern of gene expression is created as the final result (Lal et al. 1999; Abba et al. 2004; Tuteja and Tuteja 2004; Margulies et al. 2005; Wang 2007; Cheng et al. 2013; Hitzemann et al. 2014).

There are a number of sub-SAGE classes which have a list of application; however, their full discussion is beyond the scope of this chapter:

- LongSAGE: this technique uses 21-bp nucleotide sequence tags (bp: base pair) instead of the original SAGE technique that analyzes 14 bp's. it is considered that about 80% of the human transcriptome could be covered using SAGE with 14 bp's while about 99.8% are estimated to be assessed using LongSAGE; however, LongSAGE has a number of limitations which has led to development of more advanced SAGE generations (Saha et al. 2002; Wei et al. 2004; Wahl et al. 2005; Dyhrman et al. 2006)
- Robust-LongSAGE (RL-SAGE): is an updated technique compared to LongSAGE with the capacity to perform "high-throughput" transcriptomic assessments. RL-SAGE has increased efficiency in concatemer cloning and increased capacity for clone insert size, creating a library which contains more than 150,000 clones; RL-SAGE could recover all the technical troubles in SAGE and Long-SAGE including "low cloning efficiency" and "small insert sizes" (Gowda et al. 2004; Gowda and Wang 2008)
- SuperSAGE: uses 26 base-pair tags from cDNA which is the longest tag size of in all SAGE modalities; this is why novel genes in all eukaryotic could be identified by this technique. Besides, SuperSAGE uses typeIII restriction enzyme EcoP15I as tagging enzyme; this technique is the most improved variant in all microarray modalities (Matsumura et al. 2005, 2008a, b)
- Other techniques like MAGE, SADE, microSAGE, miniSAGE, deepSAGE all of them are new modifications of SAGE which help researchers perform micro-assessments of transcriptome in different cell populations; both in health and disease (Tuteja and Tuteja 2004; Wang 2007; Anisimov 2008; Nielsen 2008)
- Cap Analysis of Gene Expression (CAGE): another technique used in transcriptomics introduced by Shiraki et al., in 2003 which is characterized by "preparation and sequencing of concatamers of DNA tags from 5′ end mRNAs", used mainly for assessment of the promoter structure (Shiraki et al. 2003)
- RNA-sequencing (or next-generation sequencing) is the relatively newly introduced technique; which is used for large-scale transcriptomic studies and applied clinical sequencing. Using massively high throughput sequencing data, this method has a number of novel applications and great advantages like producing

deep profiles of the transcriptome and differentiating between physiologic and pathologic states (Schuster 2008; Birol et al. 2015; Park and Kim 2016; Qin 2019)

- Massively Parallel Signature Sequencing (MPSS): this method of transcriptomics has a number of specific features (Brenner et al. 2000; Reinartz et al. 2002; Torres et al. 2008; Hitzemann et al. 2014)
  - MPSS is an open-ended platform; identity of RNA molecules is not predefined (in contrary to microarray gene expression techniques)
  - gene expression level is analyzed in MPSS by mRNA molecules' count; the total mRNA molecules produced by each gene

Most of body functions are dependent on the integrity and function of the proteins. First coined in 1995, Proteomics is the study of body proteins and their characteristics in large-scale methods; including their structure, function and concentration, during health and disease in samples of a cell, a tissue or an organ or any other biological sample. PROTEOMICS is based on a combination of two concepts: PROTEins and genOME; in other words, proteomics assesses a complete set of "all proteins encoded by the genome"; i.e. a wide range assessment of structure and function of the proteome. The ultimate goal is to assess all proteins of a cell or organ, etc. in combination together instead of studying each protein separately and so, finding an integrated and holistic view regarding structure and function of the biological proteins (Atkins and Johansson 2006; Li et al. 2017).

Every human being has his/her unique genome; however the study of genome would not be sufficient per se for diagnostic and/or therapeutic targets; since different proteins are produced from genome based on time, tissue of origin and the collection sample, leading to the use of proteomics based diagnosis and pharmaco-proteomics. Meanwhile, proteomic studies do not have a restriction in the quantity of the contemporarily assessed molecules. The main applications of proteomics discussed in Tables 2.3 and 2.4 (Wilkins et al. 1996; James 1997; Atkins

Table 2.3 The main approaches of proteomics (Chandramouli and Qian 2009)

	Approach	Examples in anesthesiology and perioperative medicine
1	Profiling of the proteome (qualitative vs. quantitative)	• Assessing the effects of remote Ischemic Preconditioning (Hummitzsch et al. 2019) • Proteomic profiling of maternal serum of pregnant mothers with preclinical and clinical eclampsia (Rasanen et al. 2010)
2	Comparing two or more protein samples regarding their protein expressions	Comparing the levels of AMBP (alpha-1-microglobulin/bikunin precursor) protein in cerebrospinal fluid (CSF) of normotensive pregnant women and women with preeclampsia (Ma et al. 2014; van den Berg et al. 2017)
3	Detection of posttranslational modifications (PTM): both localization and identification of PTM	The role of PTM of cardiac proteasomes on ischemia, hypertrophy and atrophy of myocardial cells in different cardiac diseases and perioperative cardiac hazards (Zhao and Jensen 2009; Scruggs et al. 2012)
4	protein–protein interactions (assessment, identification and evaluation)	cerebral hypoxia-ischemia induced expression of the biotin analogue 2-iminobiotin (2-IB) and the afterwards cell stress regulation (Zitta et al. 2016)

Table 2.4 The main proteomic study methods (Blackstock and Weir 1999; Graves and Haystead 2002; Yanagida 2002; Atkins and Johansson 2006; Au et al. 2007; Jain 2010a, 2010b; Ku et al. 2016; Li et al. 2017; Woo et al. 2020)

Modality name	Description of the modality	Application of the modality
Expression proteomics	This modality assesses the global protein expression and its changes	• disease markers • data collection and analysis for toxicological and drug interaction • discovering targets for new drugs • assessment of the effects of biological agents on cell function and cell homeostasis • authentication of biomarkers, mainly in 3 fields: diagnosis, prognosis, predictive and prognostic issues
Functional proteomics	This modality assesses the function of the proteome; including: • enzyme activities • protein/protein interactions • post-translational modifications	Assess the function of proteins like enzyme functions, protein activity, etc.
Structural proteomics	Detecting the structure of the proteins: • their folding • tertiary structure • quaternary structure	Detection of the protein structures in different cells, organs and tissues
Cell-MAP proteomics (MAP = Magnified Analysis of the Proteome)	In-situ assessment of the protein effects and interactions	• multiscale super-resolution imaging of subcellular architectures • ultrastructural characterization of cell structures • determining the molecular identity of each single cells (Ku et al. 2016; Woo et al. 2020)

and Johansson 2006; Chandramouli and Qian 2009; Ercole et al. 2017; Nandal and Burt 2017).

Proteomics is technologically composed of 3 main pillars (Gulcicek et al. 2005; Chandramouli and Qian 2009; An et al. 2019):

1. A *fractionating* technology to cleave complex proteins
2. *Mass Spectrometry* technology for receiving the needed data of protein structure
3. *Bioinformatics* technology for data analysis and data assembly; today, this pillar is the fastest growing part of proteomics

The following topics could be mentioned as the main clinical applications of proteomics in Personalized Anesthesia and Perioperative Medicine:

- The expression of proteins is specifically affected in diseases and after drug administrations; so, one of the most important targets of proteomics is to study

protein expression and its alterations in an inclusive, complete and quantitative way under physiologic and non-physiologic circumstances. In this field, the cellular and subcellular proteins and enzymes involved in the energetics of the cell could be assessed using proteomics; both in disease and health. During perioperative ischemic-reperfusion injury, posttranslational modifications of the myocardial proteins are significantly increased. Besides, proteomics studies are a suitable tool for assessment of Ischemic Preconditioning (IPC) in myocardial cells; a process that is highly intermingled with perioperative cardiac effects of anesthetic drugs (White et al. 2005; Kim et al. 2006; Fert-Bober et al. 2008; Schaub et al. 2009; Zhao and Jensen 2009; Scruggs et al. 2012; Wang et al. 2016; Hummitzsch et al. 2019).

- Novel modalities for treatment emerge out of OMICS studies; for example in pediatric congenital heart diseases or in failing/ischemic myocardial cells, the newly emerged method of autologous mitochondrial transplantation has been really promising for therapeutic purposes; proteomics is one of the main methods for monitoring and management of these novel treatments (McCully et al. 2016; Emani and McCully 2018; Doulamis et al. 2019; Guariento et al. 2019; Moskowitzova et al. 2019; Shin et al. 2019; Blitzer et al. 2020)
- A large number of body proteins are considered as "drugable proteins"; however, just a minority of these proteins could be used as targets for drug effects (Max and Stewart 2008; Jimenez and Galinkin 2015; Nandal and Burt 2017)
- A significant contribution of proteomics in personalized medicine is the role of biomarkers in diagnosis and monitoring of diseases, assessing the drug effects and as alternate measure for clinical outcome measures; patients with sepsis or septic shock are good examples of infectious inflammation who benefit in diagnosis, treatment, follow up and prognosis form proteomic assessments (Lu et al. 2006; Claus et al. 2010; Reinhart and Hartog 2010; Prucha et al. 2017; Peters van Ton et al. 2018; Průcha et al. 2018)
- Pain is among the most dramatic experiences in all patients in perioperative period; it is also a main challenge for anesthesiologists to suppress acute and chronic pain efficiently; proteomic studies not only help us create novel analgesic drugs but also give more vivid guidance to anesthesiologists and other clinicians to suppress pain in a more complication-free and more effective method; i.e. personalized management of pain (Alzate et al. 2004; Max and Stewart 2008; Niederberger and Geisslinger 2008; Chidambaran and Sadhasivam 2012; Jimenez and Galinkin 2015; Mackey 2016; Moore and McCrory 2017; Konig et al. 2019; Sankarasubramanian et al. 2019)
- Central nervous system is among the most sensitive organ systems of the body. Any injuries to the system due to the underlying disease or due to unwanted perioperative complications may lead to major morbidity and increase the risk of perioperative mortality. OMICS studies in general and specifically proteomic studies improve our capabilities to monitor and treat these specific challenges; in different pathologic states like traumatic brain injuries, Synaptotoxic, neurotoxic and neurodegenerative brain damage, dysfunctional cerebral metabolism, neurocognitive outcomes especially after high risk surgeries (i.e. cardiac surgeries),

neuro-rehabilitative interventions (LoPachin et al. 2003, 2008; Wolahan et al. 2015; Ercole et al. 2017; Yang and Paschen 2017; Song et al. 2018; Sowers et al. 2018; Wang and Yang 2019).

Based on the different aspects of protein expression, structure and function and also, the interactions of proteins inside cell (in the cellular and subcellular structures), the proteomic study methods could be divided to a number of main fields which are discussed in brief in Table 2.4.

The science and techniques attributed to metabolomics are defined as the process of studying the molecules and metabolites (in all sizes) that are products of biological or pathological processes in cells, tissues, organs and the whole body. Metabolome is the sum of the molecules that yield to phenotype (phenome) which include amino acids, lipids (lipidomes), sugars (glycomes), and other molecules. They could be endogenous molecules or exogenous ones (like environmental, drug-related, nutritional and toxic molecules). The same as other OMICS fields, metabolomics depends on sophisticated technology combined with Information Technology (IT) and artificial intelligence (AI) (Rush and Ibrahim 2018; Chen et al. 2019; Sakaguchi et al. 2019; Srivastava 2019; Mordaunt et al. 2020).

Roger Williams and his colleagues in late 1940's introduced a paper chromatography method that was named metabolomics later (Gates and Sweeley 1978). In 1970's, Horning and co-workers and also, Pauling and Robinson and their colleagues used Gas Chromatography Mass Spectrometry (Horning and Horning 1971). A decade later, high-resolution/sensitivity Mass Spectrometry and nuclear magnetic resonance (NMR) were developed; followed by progressive IT based analyses reaching to the current metabolomic techniques that give us great diagnostic, prognostic and monitoring capabilities (Griffiths and Wang 2009; Gowda and Djukovic 2014).

Considering the effects of metabolomics on body homeostasis, it would be clearly predictable that a great number of metabolomic fluctuations occur throughout the perioperative period. The majority of anesthetic drugs (if not all) and nearly all the surgical procedures affect the metabolomic pattern of the body. So, we can use the metabolomic profiling of patients as diagnostic, prognostic and follow up markers and also, to assess the effect of perioperative therapeutic modalities. In near future, even some of the subjective outcomes like acute and chronic pain or postoperative nausea could be measured objectively using the metabolomic assessments. Personalized tailoring of the anesthetic drugs and choosing the most appropriate one for each individual patient would be another potential and interesting application of metabolomics in perioperative period (Makaryus et al. 2011; van Velzen and Dahan 2014; Ghini et al. 2015; Moaddel et al. 2018; Qian and Wang 2020).

The prognostic value of perioperative risk stratification tests and models would be revolutionized using metabolomic studies in near future. In 1968, when Samuel Rahbar, the Iranian scientist, discovered the role of HbA1c in diabetes mellitus, he possibly could not believe one day it would be one of the most important indicator of care in diabetes mellitus; an event which occurred decades later and was a breakthrough discovery (Gebel 2012; Azizi et al. 2013).

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Chapter 3
Personalized Anesthetic Pharmacology

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Introduction

Pharmacogenomics focuses on identifying genetic variants that influence pharmacodynamics and pharmacokinetics of drugs, with the goal of understanding individual patient's drug and dose requirements based on their genetic profile. Historically, *CYP2D6* genetic polymorphisms have been associated with different rates of substrate drug metabolism (Ingelman-Sundberg 2005). Since then, the research of pharmacogenomics has increased substantially, with three approaches to genetic studies (Mooney 2015):

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- The first involving a candidate gene known to code a receptor or enzyme important for pharmacokinetics and pharmacodynamics of the studied drug,
- The second, where a genome wide association study is performed, testing a large number of markers,
- The third that is a hybrid where the exome or genome is sequenced and studied to look for novel variants that will affect pharmacogenomics.

Commercially available custom single nucleotide polymorphism (SNP) assay chips are nowadays available for anyone who wants to learn their pharmacogenetic profile and clinically utilize the findings of pharmacogenomic studies.

Personalised medicine, considering the genetic profile of the patient, lifestyle, and environmental factors, has the potential to add new value to health care and to change the current one drug-fits-all approach. This is especially relevant for the explanation of variable responses to the same drug doses, often seen in the clinical practice, like in anesthesiology (Xie et al. 2018a; Bach-Rojecky et al. 2019a).

Although efficient and safe anesthesia is grounded on clinical protocols, which take into consideration relevant procedure-related, patient-related and anesthetic drugs-related factors, dosage setting and adjustment can be made employing direct drug levels monitoring and automatic closed-loop control to achieve and maintain optimal anesthesia and reduction of perioperative complications because of optimal drug delivery to the patients. Various polymorphisms of genes encoding for anesthetic drug molecular targets, as well as their transporters and metabolic enzymes, might change a drug pharmacodynamic or pharmacokinetic characteristics, thus influencing the clinical features of anesthesia (Puri et al. 2016; Kong et al. 2020).

General anesthesia commonly combines various drugs such as volatile anesthetics, hypnotic-sedative agents, muscle relaxants, and opioid analgesics. Additionally, some other drugs are commonly used in perioperative and postoperative period, such as local anesthetics, antiemetics, non-steroidal anti-inflammatory drugs (NSAIDs), and proton pump inhibitors (Puri et al. 2016; Kong et al. 2020). General anesthetics are among the most dangerous drugs used in clinical practice because of their peculiar pharmacokinetic properties, narrow therapeutic window, and various drug-unique adverse effects profile. The majority of these effects are dose/concentration-related, like hypotension, central nervous system (CNS) and respiratory depression, or are a consequence of drug or formulation characteristics (Xie et al. 2018a; Bach-Rojecky et al. 2019a). Some of the most dangerous complications, like malignant hyperthermia, have a clear genetic background (Gonsalves et al. 2019).

In this chapter, we will give a comprehensive overview of the genetic variations possibly linked to efficacy and safety of the most commonly used drugs in anesthesiologic practice. All of the currently available clinical guidelines will be explicitly mentioned in the text.

Genetics

As previously stated, pharmacogenomics and pharmacogenetics describe the relationship between various genetic variants of an individual and drug responses on those genetic variants. The terms pharmacogenetics and pharmacogenomics can often be interchanged, however pharmacogenetics explains a single gene-drug interaction, whereas pharmacogenomics is a broader field in which multiple genes are considered (Kaye et al. 2018). It is well known that carriers involved in drug transport through different physiological barriers and enzymes that metabolize drugs are proteins, as well as most drug target receptors. The core concept of pharmacogenomics is that there are various combinations of protein activity in different people due to their different genetic makeup and that there is no one-size-fits-all drug for a single condition due to this fact (Xie et al. 2018a; Bach-Rojecky et al. 2019a; Dib et al. 2018; Höppner and Primorac 2016). From that, it is easy to understand the postulate of individualized medicine: right drug, for the right patient, at the right time. In pharmacogenomics, different alleles are analyzed to find SNPs (Dib et al. 2018). SNPs make the difference in observed drug effect by modeling the activity of their protein product (metabolizing enzyme, transporter protein, drug receptor, or other proteins not directly related to the medication). It is important to emphasize the clinical value of other genes related to drug hypersensitivity reaction. For example, carriers of the variant *HLA-B*15:02* allele, are at high risk of developing phenytoin-induced Stevens-Johnson syndrome and the related toxic epidermal necrolysis (Höppner and Primorac 2016).

In the published consensus terms by Caudle et al. (2017), Clinical Pharmacogenetics Implementation Consortium (CPIC) has tried to establish a standardized method for reporting the results of molecular analysis of pharmacogenes, since the phenotypic interpretation can be assumed by different terms used to describe a variant allele's impact on enzyme function. Their argument states "For example, a genetic testing laboratory report might interpret a thiopurine S-methyltransferase *(TPMT) *3A* allele as leading to "low function," "low activity," "null allele," "no activity," or "undetectable activity." Moreover, a laboratory might assign a phenotype designation to an individual carrying two nonfunctional *TPMT* alleles as being "*TPMT* homozygous deficient" while another laboratory might use the term "TPMT low activity". These same laboratories could also use different terminology to describe a similar phenotype for a different gene (e.g., an individual carrying two nonfunctional dihydropyrimidine dehydrogenase (*DPYD*) alleles might be described as "DPYD defective". As a result, the use of inconsistent terms can be confusing to clinicians, laboratory staff, and patients (Caudle et al. 2017). This is the main cause of confusion and resistance towards implementation of pharmacogenomic findings into clinical practice (Caudle et al. 2017). For this reason, CPIC implemented standard terminology across all areas of clinical pharmacogenetics, including clinical genetic testing laboratory reporting. The standardized terms are presented in Table 3.1.

Table 3.1 Standardized nomenclature for gene-phenotype referencing

Term/gene category	Final term	Functional definition	Genetic definition	Example diplotypes/alleles
Allele functional status: all genes	Increased function	Function greater than normal function	N/A	*CYP2C19*17*
	Normal function	Fully functional/wild-type	N/A	*CYP2C19*1*
	Decreased function	Function less than normal function	N/A	*CYP2C19*9*
	No function	Nonfunctional	N/A	*CYP2C19*2*
	Unknown function	No literature describing the function or the allele is novel	N/A	*CYP2C19*29*
	Uncertain function	Literature supporting function is conflicting or weak	N/A	*CYP2C19*12*
Phenotype: drug-metabolizing enzymes (CYP2C19, CYP2D6, CYP3A5, CYP2C9, TMPT, DPYD, UGT1A1)	Ultrarapid metabolizer	Increased enzyme activity compared to normal metabolizers	Two increased function alleles, or more than 2 normal function alleles	*CYP2C19*17/*17CYP2D6*1/*1XN*
	Rapid metabolizer	Increased enzyme activity compared to normal metabolizers, but less than ultrarapid metabolizers	Combination of normal function and increased function alleles	*CYP2C1 *1/*17*
	Normal metabolizer	Fully functional enzyme activity	Combinations of normal function and decreased function alleles	*CYP2C19*1/*1*
	Intermediate metabolizer	Decreased enzyme activity (activity between normal and poor metabolizer)	Combinations of normal function, decreased function, and/or no function alleles	*CYP2C19*1/*2*
	Poor metabolizer	Little to no enzyme activity	Combination of no function alleles and/or decreased function alleles	*CYP2C19*2/*2*

Phenotype: Transporters (SLCO1B1)	Increased function	Increased transport function compared to normal function	One or more increased function alleles	*SLCO1B1*1/*14*
	Normal function	Fully functional transporter function	Combinations of normal function and/or decreased function alleles	*SLCO1B1*1/*1*
	Decreased function	Decreased transporter function (function between normal and poor function)	Combinations of normal function, decreased function, and/or no function alleles	*SLCO1B1*1/*5*
	Poor function	Little to no trasnport function	Combination of no function and/or decreased function alleles	*SLCO1B1*5/*5*
Phenotype: high-risk genotype status (HLA-B)	Positive	Detection of high-risk allele	Homozygous or heterozygous for high-risk allele	*HLA-B*15:02*
	Negative	High-risk allele not detected	No copies of high risk allele	

Accessed from: Caudle KE, Dunnenberger HM, Freimuth RR, Peterson JF, Burlison JD, Carrillo MW et al. Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC). Genet Med. 2017 Feb; 19(2): 215–223. doi: https://doi.org/10.1038/gim.2016.87. Licensed under CC BY 4.0. No changes have been made to the original

The most relevant information a clinician can be provided with when given pharmacogenomic test results is the protein phenotype. To this date CPIC has published 23 clinical guidelines designed to help clinicians optimize drug therapy according to the test results (Clinical Pharmacogenetics Implementation Consortium 2019). Another organization that focuses on providing clinical guidelines to genetic annotations is The Dutch Pharmacogenetics Working Group (DPWG). The guideline development process for each drug starts with a systematic literature review, then the articles included in the reference lists are individually screened for additional material or papers. Review articles, studies involving nonhuman subjects, and in vitro experiments are excluded from the scope of their review. Level of evidence of the gene-drug interaction and clinical relevance of the gene-drug interaction are defined before concluding the process with a clinical recommendation. The limitations of this process are: (1) pharmacogenetics is not the primary objective for most of the studies, therefore many of the studies are underpowered, with insufficient sample size per genotype or phenotype; and (2) the end points assessed are often the pharmacokinetic ones and the result of single-dose experiments in healthy volunteers that do not represent the conditions in daily medical practice (Swen et al. 2011).

A novel model of discovering genes directly involved in pharmacology of general anesthetics and their pharmacogenomic properties is the zebrafish, whose genome can be manipulated and utilized in research (Bedell et al. 2018).

In the following sections of this chapter we aim to give a comprehensive overview of the most commonly used drugs in anesthesiologic practice and pain treatment with an emphasis on the genes relevant for their pharmacokinetics or action or action. Note that not all of the later mentioned gene polymorphisms have a clinical guideline available at present due to a lack of high-quality scientific evidence that would support such a therapeutic intervention. Table 3.2 summarizes the genotypes discussed in this chapter and their effect on the drugs used in anesthesiological practice.

Volatile Anesthetics

Volatile anesthetics differ in their physicochemical properties, potency, and solubility in blood and tissues. Apart from those differences, speed of induction and recovery from anesthesia, as well as some specific adverse-effects profile might govern the use of one drug over others in specific situations.

Their anesthetic action is proposed to result from binding to the diverse membrane proteins, such as neuronal channels as a part of nicotinic acetylcholine (nAch), GABA-A, glutamate N-methyl-D-aspartate (NMDA), or serotonin 5-HT3 receptors, as well as voltage-gated sodium, potassium and calcium channels at higher anesthetic concentrations (Bach-Rojecky et al. 2019a).

The relevance of genes encoding for a specific receptor/channel subunit is largely under-investigated in the context of anesthetic drug action. Because of diverse potential molecular targets, it is not rational to expect that a single gene polymorphism, like SNPs for different receptor subunits, would significantly affect the

Table 3.2 A summary of drugs used in anestesiology and the genotypes influencing their pharmacologic effect

Drug class	Drug	Protein	Gene	Genotype (Important allelic variants)	Effect on drug pharmacokinetics/pharmacodinamics and clinical outcomes
Volatile anesthetics	Desflurane Isoflurane Sevoflurane	RYR1	*RYR1*	Multiple (48 variants) at 19q13.1	Safety: Increased risk of malignant hyperthermia because of Ca^{2+} leakage from the intracellular source; CPIC guideline available
		DHPR	*CACNA1S*	rs772226819 (c.520 C > T)	
				rs1800559 (c.3257 G > A)	
	Nitrous Oxide	MTHFR	*MTHFR*	rs1801133 (677 C > T)	Safety: Abnormal plasma homocysteine concentration; potential cardiotoxicity?
				rs1801131 (1298 A > C)	
Intravenous anesthetics	Propofol	CYP2B6	*CYP2B6*	rs3745274 (G > T)	Decreased metabolism of the drug; dosage adjustment (decreased dose needed)
				rs2279343 (A > G)	Decreased elimination rate from the central compartment; dosage adjustment
		5HT2A	*5HTR2A*	rs6313 (T > G)	Increased response to propofol anesthesia
	Etomidate		*GABRA1*	β2, β3, γ subunits containing	Changed receptor binding affintiy (low level evidence)
	Ketamine	CYP2B6	*CYP2B6*	CYP2B6*1	CYP2B6 *6/*6 diplotype may have decreased clearance; Safety: increased risk of adverse effects
				CYP2B6*6	
	Diazepam	CYP2C19	*CYP2C19*	CYP2C19*2	Reduced enzymatic activity; elevated diazepam concentration increased risk for adverse events
				CYP2C19*3	
	Midazolam	CYP3A4	*CYP3A4*	CYP3A4*22	Reduced enzymatic activity; increased midazolam plasma concentrations; increased risk for adverse events
		CYP3A5	*CYP3A5*	CYP3A5*1	Increased metabolism (hydroxylation) of midazolam
		$GABA_A$	*GABRA1*	187+3553 (A > G)	Increased drug affinity for the receptor; profound sedation
	Dexmedetomidine	ADRA2A	*ADRA2A*	rs1800544 (C1291G)	Change in a_{2A} receptor structure and decreased drug activity; reduced sedative effect

(continued)

Table 3.2 (continued)

Drug class	Drug	Protein	Gene	Genotype (Important allelic variants)	Effect on drug pharmacokinetics/pharmacodinamics and clinical outcomes
Muscle relaxants	Rocuronium	OATP1A2	*SLCO1A2*	rs3834939 (-189_-188InsA) -/A and A/A genotypes	A lower rate of drug elimination by the liver and slower decline in plasma concentration; prolonged duration and recovery time
		OATP1B1	*SLCO1B1*	rs2306283 (388 A > G)	
		P-gp	*ABCB1*	rs1128503; (1236 C >T)	
	Succinylcholine (Suxamethonium)	BChE	*BChE*	A-variant: rs1799807; (c.293 T > C)	Reduction of drug metabolism due to reduced enzyme activity; prolonged muscle relaxation (paralysis) and apnea
				K-variant: rs1803274 (c.1699 C > T)	
				F-variant: rs28933390 (c.1253 C > A)	
				S-variant: rs104893684 (c.1004 A > G)	
		RYR1	*RYR1*	Multiple (48 variants) at 19q13.1	Safety: Increased risk of malignant hyperthermia because of Ca^{2+} leakage from the intracellular source; CPIC guideline available
		DHPR	*CACNA1S*	rs772226819 (c.520 C > T)	
				rs1800559 (c.3257 G > A)	

Opioid analgetics	Codein Tramadol Oxycodone	CYP2D6	*CYP2D6*	Multiple (phenotype-based recommendation)	DPWG clinical guideline available on genotype-based dosing
	Tramadol	OCT1	*SLC22A1*	Number of active alleles (0, 1, 2)	Required less tramadol and have higher plasma AUC for postoperative pain with less active transporter.
	Morphine Alfentanil Fentanyl Sufentanil Ramifentanil	MOR	*OPRM1*	rs1799971 (118 A > G)	Reduced analgesic effect
	Fentanyl	CYP3A4	*CYP3A4*	*1G allele homozygots	Reduced analgesic effect
		CYP3A5	*CYP3A5*	*1 allele carriers	Increased enzymatic activity; dosage adjustment may be required
		Laminin-332	*LAMB3*	rs2076222 (C2777A) C carriers	Higher pain sensitivity
	Morphine	P-gp	*ABCB1*	rs1045642 (C3435T) rs1128503 (C1236T) rs9282564 (A61C)	Decreased excretion of drug because of reduced expression of P-gp; dosage adjustment may be required
		UGT2B7	*UGT2B7*	rs 7439366 (T802C) CC genotype	Required less morphine for postoperative pain
Local anesthetics	Benzocaine Prilocaine Lidocaine Articaine	G6PD	*G6PD*	Multiple (more than 200 variants) at Xq28	Safety: Drug-induced methemoglobinemia

(continued)

Table 3.2 (continued)

Drug class	Drug	Protein	Gene	Genotype (Important allelic variants)	Effect on drug pharmacokinetics/pharmacodinamics and clinical outcomes
NSAIDs	Ibuprofen Flubiprofen Meloxicam Piroxicam	CYP2C8 CYP2C9	*CYP2C8* *CYP2C9*	Multiple (phenotype-based recommendation)	Different rate of drug metabolism across phenotypes
	Celecoxib	CYP2C9	*CYP2C9*	Multiple (phenotype-based recommendation)	FDA-approved label, poor metabolizers should take with care
Antiemetics	Ondansetron Tropisetron	CYP2D6	*CYP2D6*	Ultrarapid phenotype	Lack of efficacy, change of medication encouraged; CPIC guideline available
	Ondansetron	P-gp	*ABCB1*	rs1045642 (C3435T), rs2032582 (G2677T)	At risk of lack of efficacy in chemotherapy-induced nausea and vomiting
				rs1128503 (C1236T) CC genotype	Higher incidence of PONV.
Proton pump inhibitors	Pantoprazole Lansoprazole Omeprazole	CYP2C19	*CYP2C19*	Multiple (phenotype-based recommendation)	Different rate of drug metabolism across phenotypes. Ultrarapid metabolizers could be at risk of lack of efficacy.

anesthesia outcomes (Bach-Rojecky et al. 2019a). Inhalational anesthetics have specific pharmacokinetic characteristic: after application, they are rapidly absorbed due to their high lipophilicity into the systemic circulation and distributed into tissues; they are minimally metabolized and almost completely excreted by lungs. Therefore, their action is not dependent on common polymorphisms of genes encoding for metabolizing enzymes, or drug transporters (Xie et al. 2018a; Bach-Rojecky et al. 2019a).

Isoflurane produces concentration-dependent profound respiratory depression and hypotension because of decreased systemic vascular resistance. It can therefore cause transient tachycardia and hypertension as a consequence of sympathetic stimulation. It is an airway irritant and because of pungent odor is not used for the induction of anesthesia. No gene-drug interactions are expected as it is eliminated by lungs almost completely (Patel 2018).

Sevoflurane induces the rapid onset of anesthesia, and is often used for induction in outpatient anesthesia. It does not irritate the airways and has a strong bronchodilator effect. Moreover, it has a stable effect on cardiac function and it doesn't influence heart rhythm (Li and Yuan 2015). There are no clinically relevant data regarding a potential nephrotoxic effect of fluoride since around 5% of the inhaled dose is metabolized in the liver via CYP2E1 to hexafluoroisopropanol and fluoride (De Hert and Moerman 2015).

Desflurane induces rapid induction and fast recovery from anesthesia and can be used for outpatient surgery. It is suitable for obese patients undergoing prolonged surgery because of its very low fat-to-blood solubility. However, due to a high incidence of moderate to severe upper airway adverse events, it is not suitable for the induction of anesthesia. It is not expected to cause nephrotoxicity as it is mostly excreted unchanged by lungs (Bach-Rojecky et al. 2019a).

Nitrous oxide gas (N_2O) is unable to induce surgical anesthetic depth alone in applied concentrations, but it is commonly used as an adjunct to halogenated anesthetics in order to reduce their effective concentrations. It produces a strong analgesic effect because of the stimulation of central opioid and adrenergic system. It also increases blood pressure, heart rate, and cardiac output due to activation of the sympathetic system (Patel 2018). However, because of its rapid entry into body cavities, which cannot be accompanied by an equally fast N_2 escape, it can increase the risk of pneumothorax, air embolus, obstruction of the middle ear, or intra-ocular air bubble due to the increased pressure in cavities (Munson 1974). Alcoholism, vitamin B12 deficiency and malnutrition are all risk factors for reduced folate synthesis and hyperhomocysteinemia when N_2O is administered as it irreversibly oxidizes the cobalt in vitamin B12 thus reducing remethylation of homocysteine to methionine with potential of causing megaloblastic aneamia, peripheral neuropathy, cell apoptosis and DNA hypomethylation. Furthermore, patients that are homozygous for methylenetetrahydrofolate reductase (*MTHFR*) and those who have 677 C > T or 1298 A > C polymorphisms are at increased risk for hyperhomocysteinemia due to a decreased folate synthesis after N_2O administration (Nagele et al. 2008). The significance of *MTHFR* polymorphisms for these N_2O adverse effects has to be further investigated in order to establish a definitive recommendation.

The most important pharmacogenetic influence on safety of volatile anesthetics and succinylcoline (SCH) is the risk of developing malignant hyperthermia (MH). Malignant hyperthermia susceptibility (MHS) may be influenced by 1 out of 50 polymorphisms in *RYR1* gene encoding for ryanodine receptor on the membrane of sarcoplasmic reticulum and the *CACNA1S* gene encoding for a specific subunit of calcium channel (Gonsalves et al. 2019). For individuals with SNPs in the stated genes, SCH and volatile anesthetics should be avoided due to increased MH susceptibility. The diagnosis of MHS is made by one of two criteria:

1. positive response to an in vitro muscle bioassay, such as the in vitro contracture test (IVCT), or the caffeine-halothane contracture test (CHCT), as it is known in the United States; or
2. the presence of a pathogenic variant in *RYR1* or *CACNA1S* found by molecular genetic testing (Rosenberg et al. 2003).

MHS is inherited in an autosomal-dominant pattern, therefore a heterozygous genotype of a pathogenic variant of *RYR1* or *CACNA1S* can be considered as diagnostic for the trait (Gonsalves et al. 2019).

The *RYR1* variants associated with MHS make mutant RYR1 channels more sensitive to activation. The exact mechanism by which MHS pathogenic variants cause MHS is not known but current evidence strongly suggest that these variants render RYR1 channels hypersensitive to activation by depolarization by volatile anesthetics and SCH. CPIC has developed a clinical guideline for interpretation of the aforementioned genetic test findings (Gonsalves et al. 2019).

Intravenous (Parenteral) Anesthetics

Intravenous anesthetics can be applied for induction and maintenance of general anesthesia. They are small, highly lipophilic compounds sharing a similar pattern of distribution and redistribution into tissues. The speed of recovery from anesthesia is determined by the amount of drug in peripheral tissues and its rate of metabolism and elimination. Optimal dosing should be carefully determined taking into account patients health status, age, and concomitant therapy, but also a specific genotype for certain drugs, such as propofol (Bach-Rojecky et al. 2019a).

Propofol is the most commonly used parenteral anesthetic possessing sedative-hypnotic, anxiolytic, anticonvulsant, anti-inflammatory, antiemetic, antioxidative, and possibly neuroprotective effect. It activates GABA-A receptors, blocks NMDA glutamate receptors and interferes with calcium influx into cell. The adverse effects of propofol include bradycardia, hypotension, loss of airway reflexes, apnea, but tolerability as well as susceptibility to anesthetic effect vary significantly between patients, possibly as a consequence of specific polymorphisms in genes encoding for propofol molecular targets or enzymes involved in its elimination (Bach-Rojecky et al. 2019a). A study conducted by Zhong and colleagues found that carriers of the minor allele (G) in the gene for 5HT2A (SNP rs6313) required less propofol and

had a 40% decrease in the time needed to induce anesthesia. Their results also demonstrated an association of *GABA-A1* SNP rs2279020 and the sodium channel gene *SCN9A* SNP rs6746030 with depth of anesthesia, while mutations in *GABA-A1* rs2279020, *GABA-A2* rs11503014, and cholinergic muscarinic receptor—*CHRM2* rs1824024 were associated with cardiovascular susceptibility to propofol (Zhong et al. 2017).

Variable response to propofol might be a consequence of polymorphisms in genes encoding for metabolic enzymes CYP2B6, one of the most polymorphic *CYP* genes with more than 100 known SNPs, and uridine 5'-diphospho (UDP)-glucuronyltransferase (UGT), as 70% of propofol is conjugated to glucuronide by UGT1A9 while the other 30% of the drug first undergoes hydroxylation via CYP2B6 (Pharmacogene Variation Consortium 2020; Bach-Rojecky et al. 2019a). Model-based dosing simulation for *CYP2B6* SNP rs2279343 suggested that a 50% decrease in propofol infusion dose in AA and AG patient genotypes would reduce the risk of too high propofol exposure and possible adverse effects. Modeling is the step in a right direction for implementation of proactive pharmacogenetic testing, but should be reinforced by further studies (Eugene 2017).

Etomidate has a favorable effect on cardiovascular system, which is why it is primarily used in patients who are at greater cardiovascular risk (Wagner et al. 2014). It inhibits the 11-β-hydroxylase enzyme thus reducing cortisol and aldosterone synthesis in the adrenal gland, which may be harmful for the survival of critically ill patients, especially those with sepsis or septic shock. Etomidate primarily activates GABA-A receptors, while biotransformation involves hydrolyzation by hepatic esterases to inactive metabolites that are excreted by urine (Forman 2011). Genetic contribution to etomidate effectiveness and safety profile was investigated in a study, with uncertain clinical relevance, which suggested that GABA-A receptors containing β2 and β3 subunits as well as γ are sensitive to etomidate as some SNPs significantly affected etomidate binding affinity (Desai et al. 2009).

Ketamine, in contrast to other parenteral anesthetics, can be applied intramuscularly, orally, rectally, and intranasally, which can be useful in uncooperative patients or those with limited intravenous access. Furthermore, it exerts a strong analgesic effect, increases the heart rate, blood pressure, cardiac output and has a bronchodilatory effect. It produces hypnosis and amnesia without disabling patients of being able to breathe spontaneously. However, adverse drug reactions including behavioral changes, lacrimation, salivation, increased overall muscle tone, spontaneous movement of extremities, and also hallucinations, delusions, vivid dreams limit its use (Bach-Rojecky et al. 2019a). Ketamine is a non-competitive antagonist of glutamate NMDA receptors, although it has other lower-affinity pharmacological targets. It is extensively metabolized by CYP3A4, and to a lesser extent by CYP2B6 to the pharmacologically active norketamine which is later glucuronidated and eliminated via the kidney (Peltoniemi et al. 2016; Zanos et al. 2018). Although a study by Li et al. (2015) associated *CYP2B6*6* allele with decreased clearance and increased plasma ketamine concentrations leading to a higher incidence of adverse effects in chronic pain patients, stronger data regarding relevance of this specific genotype is warranted.

Barbiturates

Barbiturates such as amobarbital, pentobarbital, secobarbital alter the activity of GABA-A and glycine receptors, thus causing CNS depression and sedation which was previously used in preoperative anesthesia. Since their usage can cause respiratory depression, they have been replaced by benzodiazepines which have a safer pharmacologic profile (Xie et al. 2018a; Bach-Rojecky et al. 2019a).

Today, thiopental is the only thiobarbiturate still in use for induction of anesthesia. It has a strong sedative and hypnotic effect, rapid onset and ultra-short duration of action as a consequence of very high lipid solubility. It is extensively metabolized in the liver in several steps (desulfuration, N-dealkylation to the active pentobarbital) and excreted in urine. After prolonged infusion more than 24 h is needed for a full recovery from anesthesia because of rapid thiopental redistribution from CNS and slow elimination from the peripheral fat tissue where it accumulates. Thiopental increases the time in which GABA-A associated chloride channels are in open state, while higher doses can directly activate the channel opening (Patel 2018). Additionally, thiopental modulates the nAch receptor and Ca^{2+}-ATP-ase involved in Ca^{2+} homeostasis. Pharmacogenomic effects on thiopental are still unknown, despite its long history of use (Xie et al. 2018a; Bach-Rojecky et al. 2019a).

Benzodiapines

Benzodiazepines, like midazolam and diazepam, are positive allosteric modulators of GABA-A receptors that exert a strong sedative-hypnotic effect. Due to their favorable pharmacological and safety profile, they have taken the place of barbiturates in preoperative anesthesia. Other indications for benzodiazepines include anxiety and convulsions. Drugs in benzodiazepine group vary in receptor binding site affinity and subunits selectivity, and considerably differ in their pharmacokinetic properties. Therefore, they have different potency, as well as onset and duration of action. Benzodiazepines are mostly metabolized by cytochrome P450 enzymes and UGT. Elimination of benzodiazepines is affected by patient-related factors: older age, lower amount of fatty tissue, decreased renal and liver function are all known to slow down their elimination (Griffin et al. 2013). Polymorphisms of GABA-A receptor subunits, especially α subunits, have been identified as a point of interest for pharmacogenomic research, as it contains the binding site for benzodiazepines. Patients with AA genotype on rs4263535 in *GABRA1* (alpha-1 subunit of GABA receptor) are at an increased risk for profound sedation, but more studies are needed to confirm the clinical significance of this observation (Choi et al. 2015).

Diazepam undergoes hepatic biotransformation by CYP3A4 and CYP2C19. Its metabolites are pharmacologically active molecules that are the substrate for glucuronidation which is the final process of diazepam metabolism. Polymorphisms of *CYP2C19* have been found to decrease the metabolism of diazepam. Patients who

have a poor metabolizer phenotype have decreased metabolism of diazepam, which in turn prolongs the sedation effect and increases the risk of toxicity (Dean 2016).

Midazolam is metabolized by CYP3A4 and CYP3A5 followed by glucuronide conjugation. Its major metabolite is pharmacologically active as the parent drug. *CYP3A4* and *CYP3A5* polymorphisms are known to influence the rate of their substrate metabolism, however the available literature doesn't directly associate this enzymatic function with midazolam efficacy and safety (Bach-Rojecky et al. 2019a). Therefore, there is a need for studies correlating individual CYP phenotypes with direct clinical effect of midazolam.

Dexmedetomidine

Dexmedetomidine is a selective agonist of α2A adrenergic receptor (ADRA2A) either pre- or post-synaptically in locus coeruleus that can be used for sedation and analgesia. It is metabolized in the liver by CYP2A6 and UGT and is also highly bound to blood proteins. Therefore, different factors such as body weight, fat-free mass, hypoalbuminemia, and cardiac output should be considered before drug administration. Reviewed studies did not demonstrate any relevant SNP of genes affecting pharmacokinetics of dexmedetomidine (Bach-Rojecky et al. 2019a). However, several gene polymorphisms were found to be relevant to dexmedetomidine pharmacodynamic properties. SNP rs1800544 genotypes GG or GC in *ADRA2A* cause a decreased sedative response in patients when compared to CC genotype (Yağar et al. 2011). The clinical relevance of these polymorphisms needs further confirmation.

Neuromuscular Blocking Agents (NMBs)

Non-depolarizing drugs act as competitive antagonists of nicotinic acetylcholine receptor (nAChR), whilst the depolarizing drugs act as acetylcholine (Ach), first briefly depolarizing the membrane of muscle cells which is followed by receptor desensitization.

Within the non-depolarizing drugs, there are several pharmacokinetic differences. Regarding drug elimination, caution should be paid to patients with liver and kidney impairment. In patients with liver cirrhosis rocuronium clearance might be reduced as it is completely metabolized in the liver (Van Miert et al. 1997). Rocuronium is eliminated mostly unchanged by biliary excretion, which is reliant on hepatocellular transport by organic anion transporting polypeptide (OATP) and 1A2 (OATP1A2) and OATP1B1. Because these transporters are prone to genetic polymorphisms, recent efforts have been made to study the effect of genetic polymorphisms on NMBs pharmacokinetics. SNP rs3834939 is of particular interest in *SLOC1A2* gene that encodes OATP1A2 as it effects rocuronium elimination.

Patients that have -189_-188InsA -/A and A/A genotype may have decreased rocuronium clearance compared to those with −/− genotypes (Costa et al. 2017). Polymorphisms in solute carrier organic anion transporter family member 1B1 (*SLCO1B1*) and ATP binding cassette subfamily B member 1 (*ABCB1*) have been found to influence the duration and recovery time of rocuronium. *ABCB1* TT genotype on rs1128503 and *SLCO1B1* AG and GG genotypes on rs2306283 decrease hepatic metabolism of rocuronium which can cause its accumulation in plasma (Bach-Rojecky et al. 2019a).

Succinylcholine (SCH) is hydrolyzed by butyrylcholinesterase (BChE) to succinylmonocholine, succinic acid, and choline. Deficiency of BChE prolongs the effect of succinylcholine up to several hours, while certain genetic polymorphisms can alter its activity and cause serious adverse reactions (Andersson et al. 2019). Most of BChE polymorphisms result in reduced enzyme activity and consequently increase the duration of drug action. These polymorphisms have been observed over half a century ago and some of the most common and significant variants are: A—atypical, K—Kalow, F—fluoride and S—silent. All of these variants prolong the duration of SCH induced neuromuscular block, as they impair its degradation, therefore the use of SCH should be avoided in these patients (Bach-Rojecky et al. 2019a; Lehmann and Liddell 1969). SCH shares the risk for malignant hyperthermia with volatile anesthetics, with the same genetic susceptibility in the background (Gonsalves et al. 2019). Therefore, patients with SNPs in the *RYR1* and *CACNA1S* genes should not be given succinylcholine.

Opioid Analgesics

Opioids have been the most commonly used analgesics for about two centuries. They are metabolised in the liver by cytochrome P450 enzymes: CYP2B6, CYP2D6, CYP3A4 and CYP3A5. They bind to the μ opioid receptor (MOR) and cause analgesia. Moderate quality evidence has shown that the variability of the analgesic effect is affected by genetic variants in *OPRM1* gene encoding MOR, *ABCB1* encoding P-gp transporter, and catechol-O-methyltransferase gene (*COMT*). Over 100 allelic variants of *OPRM1* that potentially influence the effect of opioid analgesics have been identified. One of the most studied SNPs is rs1799971 (118 A > G), which results in Asn to Asp substitution (Vieira et al. 2019). The frequency of the *OPRM1* 188 A > G variant shows interethnical differences, with the highest frequency among individuals of Asian ancestry (35–50%), and lesser frequency among individuals of European (15.4%), Hispanic (14%) and African ancestry (4.7%) (Bach-Rojecky et al. 2019b).

A recent study using machine-learning algorithms to determine significant factors associated with recovery from surgery in order to develop an algorithm for estimating recovery time from general anesthesia had found that *OPRM1* rs1799971 and *ABCG2* rs2231142 are significantly associated with prolonged recovery time (Xie et al. 2018b).

Polymorphisms of *COMT* have been found to influence the efficacy of analgesic drugs. COMT metabolises catecholamines and causes upregulation of opioid receptors when its activity is reduced by altering adrenergic and dopaminergic activity (Sadhasivam et al. 2014). The most studied functional SNP of *COMT* is rs4680, where A > G transition results in a Val to Met aminoacid substitution, and lower enzymatic activity (Kambur and Männistö 2010). As it does not directly influence the pharmacological effect of opioids, more clinical evidence is needed to correlate opioid therapeutic dose range and *COMT* polymorphisms, preferably including other genes relevant to opioid pharmacokinetics and pharmacodynamics.

ABCB1 polymorphisms, coding for P-glycoprotein, can influence the effect of morphine. In a review by Xie and colleagues, mutations in *ABCB1* were associated with altered concentrations and effect of morphine. Patients carrying rs1128503 (C1236T) and rs1045642 (C3435T) alleles were found to require less morphine to achieve adequate postoperative pain relief, while patients with rs9282564 (A61C) are at increased risk for respiratory depression (Xie et al. 2018a).

Further research is needed to establish the clinical relevance of this gene polymorphism.

Fentanyl and its parenteral analogs sufentanil, remifentanil, and alfentanil are synthetic opioids commonly used for anesthesia. All of these drugs are full agonists of MOR that possess a strong analgesic effect and are therefore used in peri- and postoperative period. The effect of opioid analgesia minimises pain-evoked hemodynamic changes in patients undergoing surgery and reduces the anesthetic requirements in combination with propofol (Sridharan and Sivaramakrishnan 2019). They differ in potency and the duration of effect. The drug of choice primarily depends on desired duration of analgesic effect (Shafer and Varvel 1991): fentanyl rapidly achieves its effect in bolus doses, after small bolus doses this effect is terminated after 30 min; sufentanil's effect is terminated after 20 min. After prolonged administration recovery time varies considerably (Bach-Rojecky et al. 2019a).

Fentanyl is metabolized by CYP3A4 and CYP3A5 in the liver and has no active metabolites. Polymorphisms of *CYP3A4* were found to influence requirements for and effect of fentanyl. Patients homozygous for *1G allele required higher doses of fentanyl to achieve adequate analgesia in a low powered study (Dong et al. 2012). Similarly, lower analgesic efficacy was observed in patients carrying the *1G allele (Yan et al. 2018). Carriers of at least one functional *CYP3A5*1* allele have better fentanyl metabolism (Xie et al. 2018a). The literature regarding *ABCB1* polymorphisms and fentanyl is conflicting. rs 1045642 AA genotype seems to be correlated to a lower fentanyl dose requirement but contradicting results were reported as well (Bach-Rojecky et al. 2019a). The same observations have been made for the effect of *OPRM1* polymorphisms on fentanyl and morphine requirements (Bach-Rojecky et al. 2019a). Polymorphisms of *LAMB3* that encodes a subunit of laminin-332 (a component of the dermal-epidermal junction) on rs2076222 (C2777A) are also connected to opioids sensitivity, with patients carrying the C allele requiring more fentanyl for postoperative pain. Mutations of laminin-332 cause junctional epidermolysis bulosa (Kiritsi et al. 2013; Mieda et al. 2016).

Remifentanil is a potent and short-acting opioid analgesic. Unlike other synthetic opioids it is metabolized by non-specific plasma and tissue esterases (Beers and Camporesi 2004). Remifentanil also exerts its analgesic effects by binding to MOR. It has a duration of action <10 min and low potential for accumulation, making it suitable for brief painful procedures (Stroumpos et al. 2010). Polymorphism of *OPRM1* and *ABCB1* influence the requirements of ramifentanil in the same manner as morphine. *ABCB1* 1236 C > T CC genotype had better anesthetic effect and *OPRM1* rs1799971 AA genotype require lower doses of ramifentanil to achieve analgesia (Al-Mustafa et al. 2017; Shi et al. 2017).

Morphine can be considered a typical representative of the opioid drug group. It undergoes glucuronidation in the liver by *UGT2B7* and is then eliminated in urine. *UGT2B7* polymorphisms have been studied and they showed difference in inter-patient rate of metabolism, but to an inconclusive overall effect (Smith 2009). Another more recent study demonstrated that patients with *UGT2B7* T802C CC genotype required lower doses of morphine compared to TC and TT genotype (Bastami et al. 2014). Morphine is a full agonist of MOR, therefore polymorphisms of *OPRM1* have been recognised as important for its pharmacologic effect. As stated prior in the text, the most studied SNP of *OPRM1* is rs1799971. Studies have shown that patients with *OPRM1* rs1799971 genotype AA need lower doses of morphine to achieve adequate analgesia, while patients that carry G allele demonstrate higher pain levels (Xie et al. 2018a). When treating pain, MOR variants should be taken into account for personalized medicine, however no guidelines are yet available for use in clinical practice. Clinical studies that would support this evidence are needed to develop firm guidelines. Polymorphisms in *ABCB1* altered the effect of morphine, as described previously in the text.

Codeine is metabolised in the liver by CYP2D6 into morphine. Tragic case reports of neonate death that was breast-fed by a codeine consuming mother is a reminder that drug prescribing should account for the individual patient on a case-to-case basis (Willmann et al. 2009). Therefore, CYP2D6 mediated metabolism is a key point in safe codeine prescribing, as it could advise the clinician on patient-specific dosing requirements. Patients whose *CYP2D6* genotype results in a poor metabolizer phenotype should be given an alternative analgesic as codeine therapy would be ineffective. Ultrarapid metabolizers should be prescribed a different analgesic as the increased enzymatic activity can cause adverse drug reactions related to increased doses of morphine. The alternative analgesic drug should not be the substrate of CYP2D6 making tramadol and oxycodone unsuitable alternatives (Crews et al. 2014).

Tramadol is often prescribed for its analgesic effect. It is metabolized by CYP2D6 in the liver to its pharmacologically active metabolite O-desmethyltramadol. O-desmethyltramadol has higher affinity to opioid receptors than tramadol itself. Genotype changes in *CYP2D6* that result in its phenotype changes should be taken into account when prescribing tramadol as they can change its effectiveness and potentially cause adverse drug reactions or insufficient pain relief. Patients that are poor metabolizers should use an alternative drug as they could experience inadequate pain relief. Intermediate metabolizers can use tramadol in regular doses but should be informed that they could also

experience inadequate pain relief. For ultrarapid metabolizers, a reduction in dose of 60% or alternative analgesic are suggested (Pharm GKB 2020). The utility of *CYP2D6* genotype guided dosing of tramadol in clinical practice is evident as it can help avoid unwanted adverse reactions and prevent ineffectiveness of pain therapy. Additionally, organic cation transporter 1 (OCT1) has also been linked to tramadol effectiveness. OCT1 is a transporter in hepatocytes that mediates O-desmethyltramadol metabolism. Patients that have no active alleles had to take less tramadol for postoperative pain relief compared to patients who had 1 or 2 active alleles as demonstrated in a study that focused on postoperative pain therapy. It should be noted that pain intensity did not change in regard to the number of *OCT1* active alleles (Stamer et al. 2016).

Oxycodone is metabolised by CYP3A4 and CYP2D6 in the liver. CYP3A4 metabolism inactivates oxycodone, while CYP2D6 metabolises oxycodone to oxymorphone which is pharmacologically active. Genotype changes of *CYP2D6* that result in a phenotype of a poor, intermediate or ultrarapid metabolizer require an alternative drug as the latter can cause adverse drug reactions, while the former two phenotypes cause insufficient analgesia. The alternative drug should not be metabolised by CYP2D6, therefore tramadol and codein should be avoided in these patients as well (Crews et al. 2014; Pharm GKB 2020).

Local Anesthetics

Local anesthetics are commonly used to produce regional blockade such as spinal and epidural blocks by preventing nerve impulse transmission. They differ in physicochemical and pharmacological properties, and duration of action. Their primary binding site is in the open sodium channel inner pore, meaning the drugs must cross the cell membrane to exert their pharmacologic function. Local anesthetics are frequency and voltage dependent, making the drugs bind better to channels which open more frequently and on membranes with more positive resting potentials. Their adverse effects are dependent on the concentration in the blood after systemic absorption and are the result of interference with impulse generation and conduction in excitable tissues, such as the CNS and the heart muscle. These drugs differ in their chemical structure (esters or amides), therefore their clearance is dependent on different mechanisms. Lidocaine, bupivacaine, levobupivacaine that contain an amide group are dependent on the hepatic metabolism by CYP3A4, while the elimination of tetracaine and procaine, which are ester-type, is dependent on plasma butyrylcholinesterase activity. Considering that the ester bonds are more prone to hydrolysis, amide-type of drugs usually have a longer duration of action (Bach-Rojecky et al. 2019a; Becker and Reed 2006).

Part of the clinical effectiveness of local anesthetics can be influenced by genetic predisposition, as well. Hypothetically, genetic mutations in voltage-gated sodium channels, which are the primary drug target, are likely to affect the efficacy of local anesthetics. An in vitro experiment has shown that Asn395Lys mutation in the

sodium voltage-gated channel alpha subunit 9 (*SCN9A*) could contribute to greater resistance to lidocaine (Cohen et al. 2012). At present no clinical studies have been conducted to prove the significance of this mutation in vivo.

There is a rare possibility of hemolytic anemia occurring after lidocaine and prilocaine application in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. G6PD is an enzyme that catalyzes the formation of NADPH, which maintains reduced glutathione within the cell, thus protecting cells from oxidative damage. The red blood cells are reliant on this process and are especially vulnerable in the case of G6PD deficiency. A literature review that focused on perioperative management of G6PD deficient patients advised against the use of benzocaine, prilocaine, lidocaine and articaine as they can potentially induce methemoglobinemia due to the fact that these patients cannot return hemoglobin to its ferrous form (Elyassi and Rowshan 2009).

Other Drugs Used in Anesthesiology

NSAIDs

NSAIDs play an important role in therapy of low to moderate intensity pain. Their main mechanism of action is the inhibition of cyclooxigenase (COX) 1 and 2 izoforms, enzymes, which results in inhibition of prostanoids synthesis. The pharmacogenetic effect in NSAID therapy is explained by polymorphisms in genes encoding for CYP2C9 and CYP2D6. *CYP2C9* allelic variants coding for a poor metabolizer phenotype *CYP2C9*2* and *CYP2C9*3* have a prevalence of 14% and 8% in the European population respectively (Bach-Rojecky et al. 2019b).

Ibuprofen

Ibuprofen is one of the most commonly used oral NSAIDs that is metabolized by CYP2C8 and CYP2C9. Studies have shown that polymorphisms in genes encoding these enzymes cause changes in ibuprofen metabolism. *CYP2C8*3* allele carriers had increased metabolism of R-ibuprofen compared to *CYP2C8*1* allele carriers. *CYP2C9*3* allele carriers had decreased clearance of ibuprofen compared to *CYP2C9*1* allele carriers and *CYP2C9*2* allele was associated with impaired metabolism of ibuprofen enantiomers (Xie et al. 2018a). Decreased metabolism and a greater exposure to the drug seem to be associated with a higher risk of adverse drug reactions such as gastric bleeding (Kaye et al. 2018). The same observed risk increase for upper gastrointestinal bleeding in *CYP2C9*2* allele carriers is present for the use of flurbiprofen, meloxicam, piroxicam as well (Bach-Rojecky et al. 2019b).

Celecoxib

Celecoxib is a selective COX-2 inhibitor with better gastrointestinal tolerability compared to non-selective COX inhibitors. It is mostly metabolized by CYP2C9. Studies have shown that *CYP2C9*3* patients had lower pain score and better functional recovery after celecoxib administration and that CYP2C9 poor metabolizers showed higher areas under the concentration-time curves and lower clearance for celecoxib than extensive and intermediate metabolizers (Bach-Rojecky et al. 2019b; Xie et al. 2018a). Hence, the FDA-approved drug label of celecoxib states that CYP2C9 poor metabolizers should take this drug with care (Celebrex 2020).

Antiemetics

Postoperative nausea and vomiting (PONV) present an important problem in clinical anesthesia. The emetic center is regulated by neurotransmitters like dopamin, opioids, and serotonin (Kaye et al. 2018). The most commonly used drugs to prevent PONV are 5-HT3 receptor antagonists, such as ondansetron and tropisetron, that are mostly metabolized in the liver by cytochrome P-450 enzymes, namely CYP1A2, CYP3A4 and CYP2D6. Variations in both *HTR3A* and *HTR3B* genes for 5-HT3 receptors were associated with PONV (Xie et al. 2018a). *OPRM1* rs1799971 polymorphism, which is important for opioid efficacy as described previously in this text, was found to be related to PONV, as well. However, the results of the conducted studies varied regarding rs1799971 *OPRM1* genotype and the incidence and severity of PONV. Larger, more powered studies in the future are needed before specific conclusions can be made (Xie et al. 2018a).

Ondansetron, a highly specific 5-HT3 receptor antagonist is metabolized by CYP1A2, CYP2D6 and CYP3A4 in the liver (Bell et al. 2017). *ABCB1* genotypes have been put into relation with the antiemetic effect of ondansetron. The most important polymorphisms in *ABCB1* are 3435 C > T and 2677 G > T/A (Farhat et al. 2013). Antiemetic effect of ondansetron has been studied in patients that underwent chemotherapy due to a high incidence of nausea and vomiting. CG (C3435T and G2677T) haplotype and 3435CC genotype were found to be associated with a higher incidence of nausea and vomiting (He et al. 2014). In addition to chemotherapy induced nausea and vomiting, *ABCB1* polymorphisms have also been studied in patients on ondansetron therapy for PONV. Patients with 3435TT and 2677TT genotypes were less likely to experience PONV up to 2 h after surgery, however, this effect did not reach statistical significance in 2–24 h postoperative period (Choi et al. 2010). In another study there was a higher observed PONV incidence 2 h after surgery for *ABCB1* 1236 CC genotype (Farhat et al. 2015).

Tropisetron is mainly metabolized by CYP2D6 in the liver, similarly to ondansetron (Kees et al. 2001). *CYP2D6* polymorphisms should be taken into account before starting tropisetron therapy in order to avoid therapeutic ineffectiveness.

Since *CYP2D6* polymorphisms can alter the metabolism of ondansetron and tropisetron and can change their clinical effectiveness, a CPIC guideline was made for their genotype guided dosing. Intermediate and poor metabolizer *CYP2D6* phenotypes are advised to take regular doses as there is insufficient evidence of a changed clinical effect based on the genotype. For ultrarapid metabolizers, on the other hand, the evidence suggests reduced ondansetron and tropisetron effectiveness. In these patients, the increased metabolism results in a reduced anti-emetic effect. Antiemetics that are not the substrate of CYP2D6 are recommended for ultrarapid metabolizers, such as granisetron, according to the guideline (Bell et al. 2017). Although other CYP enzymes contribute to ondansetron metabolism, there are substantial data to support a major role of CYP2D6 in the metabolism of ondansetron.

Proton Pump Inhibitors

Proton pump inhibitors (PPIs) are one of the most commonly used drugs in medicine. All of the drugs in this pharmacological group are metabolized by CYP2C19 and CYP3A4 and are transported by MDR1. Genes encoding for enzymes involved in PPI metabolism have a vast number of SNPs that can effect their enzymatic activity. It appears that *CYP2C19* polymorphisms play a major role in pharmacokinetics of most PPIs (rabeprazole and esomeprazol metabolism is less dependent on CYP2C19) (Karaca et al. 2017; El Rouby et al. 2018). CYP2C19 poor metabolizers had greater bioavailability than normal, rapid and ultrarapid metabolizers, and a stronger effect on gastric acid suppression, meaning that ultrarapid metabolizers could benefit from a dose increase (El Rouby et al. 2018). Different bioavailability may play an important role in the efficacy of PPI therapy, but further studies are needed in order to determine the clinical effectiveness of genetic screening (Karaca et al. 2017).

Epigenetics

It is important to emphasize that the predictive value of a single genetic variant with regard to drug response is often limited and combinations of multiple genetic variants may be involved. Besides genome composition, other factors, such as epigenetic components and environmental inputs, can affect the phenotype, which leads to a change in the clinical drug response. Epigenetic changes: DNA methylation (CpG islands), histone modification, mRNA expression (miRNAs) can influence enzymes involved in drug biotransformation (Bach-Rojecky et al. 2019a). The potential of epigenetic application in medicine is vast but has yet to be thoroughly researched. An example of an epigenetic impact on pharmacogenomic traits is the phenomenon of phenoconversion. For example, co-administration of a drug that is a strong inhibitor of drug metabolizing enzymes can significantly change the biotransformation

rate of drug substrates of the respective enzymes by the mechanism of down-regulation. Thus, an enzyme whose genotype results in a phenotype of a normal metabolizer could change its phenotype to a poor metabolizer. This effect can persist for weeks after strong inhibitors are discontinued (Shah and Smith 2015). The aforementioned phenomenon can be extended to various medical conditions, such as advanced cancer, where the activity of CYP2C19 was found to be severely compromised (Primorac et al. 2020). Changes in DNA methylation can be induced by ethanol metabolism, smoking and some medications commonly used in medical practice, such as lidocaine (Bach-Rojecky et al. 2019a). Ethanol metabolites can impact gene expression by binding to transcription factors or by modifying chromatin structure, thus inducing epigenetic changes. Chronic alcohol consumption leads to significant reduction in S-adenosylmethionine levels, which causes DNA hypomethylation. It also contributes to the formation of reactive oxygen species (ROS) and acetate by changing the balance between NAD^+ and NADH, all of which are known to impact epigenetic regulatory mechanisms (Zakhari 2013). Enzyme induction and cross-tolerance to alcohol can lead to increased dose requirements for anesthetic agents, such as propofol, thiopental, and opioids. Elevated levels of alcohol in blood cause increased sensitivity to other drugs which also bind to neuronal GABA and glycine receptors (Chapman and Plaat 2009).

Cigarete smoking releases a vast number of harmful metabolites that impact multiple organ systems. It was observed that chronic smokers need more benzodiazepines to achieve sedation. However, the incidence of PONV is lower in smokers, probably because some of the substances released when smoking have an antiemetic effect. Discontinuing smoking prior to surgical procedures has produced mixed results, with studies reporting fewer pulmonary complications, but a higher incidence of purulent sputum in patients who discontinued smoking 8 weeks before surgery. Nevertheless, it is advised that smokers discontinue their habit at best 8 weeks prior to surgery (Rodrigo 2000). In cases where preoperative discontinuation of smoking is not possible, nicotine replacement therapy can be considered as an adjunctive treatment for pain, possibly reducing the requirement for opioids (Kork et al. 2010). Epigenetics certainly deserves detailed investigation in the near future, especially in relation to individual variability in response to drugs.

Perspective

FDA advocates pharmacogenomic approaches in drug development, review, and approval. Multiple drug labeling guidance for industry, recommending the inclusion of pharmacogenomic information in Human Prescription Drug and Biological Product Labeling were published by the FDA. According to a recent study, pharmacogenomic information in drug labels can be related to indication (patient selection and efficacy), safety (adverse events), dosing (related to pharmacokinetics) or can just provide general information. At present, the FDA provides information on 362 drug-gene pairs. These data are presented throughout many different sections of

drug labeling, for instance package insert, depending on prescribing needs, making them challenging for identification (Mehta et al. 2020).

Data accumulated over time demonstrate that one of the most common causes of iatrogenic morbidity and healthcare spending annually in the USA are adverse drug reactions. Some estimates state that genetic factors contribute to as far as 10–20% of the total number of reported adverse drug reactions. Pharmacoeconomics data show that adverse drug reactions may cost the US healthcare system up to 30.1 billion dollars annually, due to increased number of hospitalizations, extended hospital stays and additional treatment and pharmacotherapy costs. These facts indicate that proactive pharmacogenomic testing has a potential to positively influence the therapeutic outcomes, while potentially reducing the cost of healthcare (Primorac et al. 2020). A person who takes a pharmacogenomic test once can have lifetime benefits. A 2016 systematic review investigating the cost–effectiveness of pharmacogenomic screening tests showed that 55% of studies concluded that pharmacogenomic testing was cost-effective, 16% of studies showed that it was cost-saving and 13% showed that it was cost-dominant (Berm et al. 2016).

Bearing in mind that the perioperative period is the most vulnerable period for the patient and that some patients require postoperative intensive unit care due to their comorbidities and/or complexity of the operation, pharmacogenomics of anesthetics deserves to be thoroughly studied. In addition to direct drug levels monitoring and automatic closed loop control, implementation of proactive pharmacogenomic testing has a potential to aid anesthesiologists to better tailor and guide their patient care with little margin for possible unexpected events. For some drugs, as discussed in the text, clinical guidelines have been developed based on collected evidence. However, the majority of genetic polymorphisms have not been studied in adequately powered clinical studies that would show exact correlation of pharmacogenomics guided treatment and both positive outcomes and cost-effectiveness. In the future, studies that incorporate pharmacogenomic data and correlate it to treatment outcomes will mark a new chapter in personalized medicine, making new clinical guidelines available.

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Chapter 4
Personalized Cardiac Anesthesia

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Introduction

Performing cardiac surgery requires the involvement of a multidisciplinary team of healthcare professionals who aim to give the patients the best recovery possible.

In order to improve cardiac surgery outcomes and the management of patients undergoing cardiac surgery in general is essential to adopt the best practice. The latter must take into account the most recent discoveries and knowledge in the scientific field.

To better implement perioperative performance in patients undergoing cardiac surgery, it is imperative to talk about personalizing medical care.

The personalization of care requires the adoption of the latest techniques and discoveries and the use of the latest technologies. Personalized cardiac surgery requires the use of validated protocols that can lead to improvements in clinical outcomes.

Enhanced Recovery After Surgery (ERAS) recommendations for cardiac surgery are the fundamental starting points in personalizing medical care since they are based on the best practice (Engelman et al. 2019).

The creation of a multidisciplinary team that not only involves the figures who usually work in the medical field but also takes into account expertise, typical of engineering and biomedical engineering which is essential in order to provide a personalized approach.

Personalizing the surgical approach in cardiac surgery does not only mean to choose the best surgical technique for the patient, but also adopting strategies based on the specific patient.

The patient and not his pathology, must be the center of his care project and healing course.

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To facilitate the consultation we have chosen to divide the chapter in three macroareas: preoperative, intraoperative and postoperative strategies.

Preoperative Strategies

Diabetes mellitus is a metabolic disease that can lead to microvascular and macrovascular complications.

An optimal preoperative glycemic control is important for patients who are candidates for cardiac surgery. Hemoglobin A1c level less than 6.5% is crucial to prevent sternal wound infection, ischemic events and other complications. Although evidence-based guidelines recommend an improved glycemic control, 25% of patients have haemoglobin A1c levels greater than 7%, and 10% have undiagnosed diabetes. A recent study demonstrated that higher level of glucose in blood is associated with a poor prognosis in terms of survival. Therefore, measuring the preoperative level of haemoglobin A1c is important for the risk stratification.

Fortunately, nowadays, personalized medicine allows tailored treatments based on patients' characteristics including genetic, environmental and lifestyle factors. In fact, personalized medicine is a form of medicine aimed to the possibility of identifying the susceptibility of each person to possible diseases, measuring the risk, customizing the therapy according to the patient's genetic constitution. So, administering the appropriate drug reduces the possibility of adverse reactions.

The American Diabetes Association (ADA) divides this disease into four categories: type 1 diabetes mellitus (T1DM), an autoimmune disease with progressive cell destruction, completely addicted on exogenous insulin; type 2 diabetes mellitus (T2DM), a combination of insulin resistance and impairment of insulin secretion; type 3 diabetes mellitus (T3DM), that includes the monogenic form; type 4, that is the gestational diabetes.

The most well-known and well-studied form of monogenic diabetes is maturity-onset diabetes of the young (MODY). In fact, for example MODY3, the most common form of MODY, is caused by a mutation in HNF1A, which encodes the transcription factor hepatic nuclear factor 1- (HNF1-), which promotes transcription of multiple genes related to glucose metabolism, insulin secretion, and insulin production. HNF1- has 55% amino acid similarity with hepatic nuclear factor 4- (HNF4-), which is mutated in MODY1. Diagnosis of MODY1 or MODY3 is important for proper clinical therapy because those patients have been found to be hypersensitive to sulfonylureas. For this, MODY1 and MODY3 patients need approximately one-tenth of the sulfonylurea dose, although this varies depending on the patient. So, sulfonylureas are the first-line treatment for MODY1 and MODY3. It has been demonstrated that genetic diagnosis of MODY1 followed by switching of treatment from insulin to sulfonylureas improved glycemic control as measured by %HbA1c.

Another example is MODY 2. In this form, we found a mutation in GCK which encodes the enzyme glucokinase. The damaging GCK mutations cause decreased

function in the glucokinase enzyme, which is crucial for pancreatic cell monitoring of blood glucose levels. As a result, MODY2 patients present with mild hyperglycemia. It must be underlined that MODY2 patients generally do not progress to the microvascular and macrovascular complications associated with diabetes mellitus at a rate greater than nondiabetic populations. So, MODY2 patients do not need pharmaceutical therapy.

A variety of medications with different mechanisms of action have been developed for glycemic control in diabetes mellitus patients.

Metformin is widely recommended as the first-line glucose-lowering agent if there is no contraindication: among the 12 different classes of drugs available for the treatment of T2D, it has high efficacy, low-cost, and minimal drug-induced toxicity such as hypoglycemia. However, a number of studies have demonstrated that the major clinically important genes related to metformin treatment are responsible for the expression of solute carrier (SLC)-type transporters: those are mainly located in human hepatocytes and renal proximal tubules and are responsible for the plasma exposure of metformin, leading to its clinical efficacy on blood glucose, glycated hemoglobin (HbA1c), and insulin sensitivity.

The use of sulfonylureas and insulin as second-line glucose-lowering drugs, recommended in many type 2 diabetes guidelines, reflects decades of research and clinical experience. The benefits correlated to sulfonylureas and insulin are offset by increased rates of hypoglycaemia and weight gain.

Data from the GoDARTS study showed that carriers of the TCF7L2 type 2 diabetes risk allele are less likely to achieve glycaemic goals in response to sulfonylureas than non-carriers, a treatment effect that was not seen for metformin. Probably, this is the best study about genetics informing pharmacological responses.

Despite concerns surrounding relative benefits versus risks of thiazolidinediones for glucose control in individuals with type 2 diabetes, these drugs attenuate disease progression in subsets of patients with nonalcoholic fatty liver disease and nonalcoholic steatosis in studies of up to 24 months' duration. Furthermore, in the IRIS trial, pioglitazone reduced the development of new type 2 diabetes and decreased the rate of fatal or non-fatal stroke or myocardial infarction over 4 years in individuals with insulin resistance and established cerebrovascular disease.

Three new classes of glucose-lowering agents—GLP-1 receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, and SGLT2 inhibitors—have been introduced in the past 13 years, extending the ability of clinicians to treat type 2 diabetes with reduced rates of hypoglycaemia, less frequent self-monitoring of blood glucose, simplified dosing regimens, and without weight gain.

GLP-1 receptor agonists analogues that act as incretine mimetics and DPP4 inhibitors that stop the degradation of endogenous GLP1 and gastric inhibitory peptide. The incretin promotion induces insulin secretion, inhibits glucagon secretion, reduces gastric emptying, and decreases appetite.

These drugs were initially developed on the basis of metabolic physiology, and the mechanisms of action and safety of SGLT2 inhibitors and GLP-1 receptor agonists were subsequently further validated by analysis of genetic variation at SLC5A2 (the gene encoding SGLT2) and GLP1R in individuals and large population studies.

Even less is known about the pharmacogenetic determinants underlying the glycaemic response to DPP-4 inhibitors or SGLT2 inhibitors. Genetic variation at rs7202877 near CTRB1/2, a known diabetes risk locus, is associated with differential insulin secretory responses to acute GLP-1 infusion and a lower HbA1c response to DPP-4 inhibitor treatment. Genetic variation and clinical biomarkers that are associated with declining β-cell function also predict the response to GLP-1 receptor agonist therapy in some populations.

To conclude, "multiomic" applications integrating genetic, metabolomic and/or proteomic data are emerging in the field of disease risk prediction model, providing information on the mutual impacts of genetic variations and metabolic differences for the early diagnosis, treatment, and prevention of various complex diseases.

So, it's time to use "precise medicine" realizing accurate disease diagnoses and selection of the most optimal therapeutic strategy for individualized treatment, and making early detection and prevention of diseases (Kleinberger and Pollin 2015; Elk and Iwuchukwu 2017; Gloyn and Drucker 2018; Heo and Choi 2019).

A low preoperative level of serum albumin is associated with an increased risk of postoperative morbidity and mortality unconnected with body mass index. In fact, it is associated with increased length of time on a ventilator, infection, acute kidney injury (AKI), expanded time of hospitalization and mortality. Therefore, hypoalbuminemia can be considered a negative preoperative index.

In fact, it has been found that optimization of albumin levels with an intensive nutritional therapy performed 7–10 days before surgery may improve the outcome of patients with albumin levels of less than 3 g/dL. Furthermore, the state of malnutrition is associated with higher risk of colorectal infections, thus it is recommended to perform a nutritional supplement in the preoperative days whenever possible.

Proteinuria/albuminuria are indexes of kidney injury in urinalysis or quantitative measurement of creatinine concentration: their values are also used for the calculation of eGFR. Unfortunately, these methods have not provided specific and accurate information about the risk of evolution of renal damage. Thus, it's necessary to find new biomarkers for an early and more accurate disease assessment: a review of possible markers is proposed below (Everett 2015; Gluba-Brzózka et al. 2017).

- Neutrophil Gelatinase-Associated Lipocalin (NGAL), also known as lipocalin-2 (LCN2), involved in the formation of renal epithelium is rapidly released by renal tubules in response to injury. For example:
  - An acute rise in urinary NGAL (determining evolving AKI) within 2–8 h of cardiac surgery has been found in studies of both paediatric and adult populations indicated;
  - The observed sensitivity and specificity for urine NGAL concentrations reached values of 1.00 and 0.98, respectively, was found to be a promising biomarker for the early detection of acute renal failure (Mishra et al. 2005).

However, a prospective observational study of 426 adults who underwent cardiac surgery demonstrated that the relationship between postoperative urinary NGAL and AKI varied with baseline renal function. Positive relationship was observed in

this study only in patients with preoperative eGFR 60 mL/min. Authors suggested that the ability of urinary NGAL to provide early and accurate identification of developing AKI was optimal in patients with normal baseline renal function (eGFR 90–120 mL/min).

- Treatment of high blood pressure is crucial in preventing and delaying the progression of CKD, while the reduction of albuminuria hampers the progression rate of renal function loss in these patients. Albuminuria is not only a symptom of renal impairment but it can also promote renal damage itself. Strategy for renal protection are a low protein diet, RAAS blockade, non-steroidal anti-inflammatory drugs and corticosteroids. In fact, they are used to lower blood pressure, decrease albuminuria, and slow progression of renal damage.
- In patients with chronic kidney disease, vascular calcification (VC) is an important risk factor which leads to increased arterial stiffness, cardiovascular disease (CVD) and finally to mortality in this group of patients. Low serum levels of fetuin A, which mediates the inhibition of calcium-phosphate precipitation and VC, has been shown to be associated with poorer survival of hemodialysis patients.
- Moreover, systemic inflammation is considered to be a factor promoting the development of vascular disease and protein energy wasting (PEW), polymorphisms within genes encoding inflammatory cytokines and their receptors may be associated with worse prognosis and higher mortality of CKD.
- SNPs within other proinflammatory cytokines predict cardiovascular disease and mortality in the uremic milieu. Polymorphism within the promoter of interleukin-6 (IL-6) gene (G allele in 174 G/C SNP) has been associated with increased comorbidity.
- Another proinflammatory cytokine, Tumor necrosis factor (TNF), influences vascular calcification through the promotion of osteoblastic differentiation.
- In patients with renal and vascular disease, renin-angiotensin system (RAS) up-regulation has been reported. Insertion/deletion (I/D) polymorphism within intron 16 of angiotensin I converting enzyme (ACE) gene is associated with have higher ACE levels in DD carriers.
- Increased levels of ACE have been shown to correlate with not only left-ventricular hypertrophy (LVH) and higher carotid intima-media thickness, but also with the rate of renal function.
- Also, polymorphism within gene encoding angiotensinogen (AGT) (Met235Thr) is associated with high AGT levels, increased risk of concentric left ventricle hypertrophy and vascular complications in renal populations.
- Studies indicate that renal diseases are influenced not only by environmental but also by genetic factors. Therefore, it seems that the analysis of genetic aspects should be a natural component of clinical and experimental studies.
- Personalization of nephrological therapy in some types of kidney disease can be achieved by using pharmacogenetics-genomic-dynamic approach or a biomarker approach: the results are promising but further studies are needed (Everett 2015; Gluba-Brzózka et al. 2017).

All ERAS protocols, except those for cardiac surgery, suggest to suspend the intake of clear fluids 2–4 h preoperatively.

Many randomized clinical trials demonstrated that a light meal can be given up to 6 h before elective procedures requiring general anesthesia, without outcome complication.

In a small recent study, a small group of patients undergoing cardiac surgery took a carbohydrate drink 2 h before general anesthesia, without increasing the risk of aspiration; on the other hand, there might be an increased risk of aspiration both in patients who have delayed gastric emptying owing to diabetes mellitus, and transesophageal echocardiography.

A complex carbohydrate drink, swallowed 2 h preoperatively, would reduce the insulin resistance, improve postoperative glucose control and increase answering of gut function.

It has been demonstrated that carbohydrate administration reduces postoperative insulin resistance and improves patient wellbeing (Nygren et al. 2015). However, these studies on the effect of the carbohydrate loading on metabolism by and on how it affects the duration of hospital stay are still controversial due to the reduced number of patients analyzed.

Insulin resistance (IR) and metabolic syndrome are risk factors for both type 2 diabetes and ischaemic cardiovascular diseases, two pathologies that are in epidemic growth worldwide. It is being demonstrating with growing evidence that exists a link between the gut microbiome and human metabolic health, with transferability of insulin resistance phenotypes through faecal microbiome transplants (Pedersen et al. 2016; Lukovic et al. 2019). These effects may partly be mediated through the metabolome. Serum levels of amino acids, most consistently the BCAAs (triacylglycerols with low carbon number and double bonds) as well as specific membrane phospholipids, have previously been associated with IR and future risk of metabolic and cardiovascular morbidities. However, the origin of the abnormal IR-associated serum metabolome is largely unknown.

The IR-associated metabolome associates with functional components of the IR-linked gut microbiome: notably the increased potential for lipopolysaccharide and BCAA biosynthesis, and reduced potential for BCAA transport into bacterial cells, methanogenesis and pyruvate oxidation.

Some studies have shown the association of fasting serum BCAA levels with incident type 2 diabetes, the normalization of BCAA levels in obese individuals after bariatric surgery and the development of IR in rats after BCAA diet supplementation. The same studies suggest a potentially causative role of the BCAAs, or their breakdown products in metabolic disorders. The reason as to why they are elevated in the first place is not well established: potential explanations include reduced BCAA breakdown in adipose tissue and liver. There are consistent relationships in data between serum concentrations of BCAAs, bacterial BCAA biosynthesis and inward transport potentials, and the severity of IR phenotypes: these relationships are reinforced by the intriguing findings that BCAAs co-vary tightly

with fasting serum metabolites known to be of microbial origin. This suggests that the gut microbiota is another independent contributing source of elevated serum BCAA levels in common human states of IR. Furthermore, positive correlations between microbial functions—including BCAA biosynthesis—and IR are largely driven by a few species only, notably *P. copri* and *B. vulgatus*, suggesting that they may directly impact host metabolism: test with mice fed a high-fat diet showed that a challenge with P. copri led to increased circulating serum levels of BCAAs, insulin resistance and an aggravation of glucose intolerance.

It can be stated that dysbiosis of the human gut microbiota impacts the serum metabolome and contributes to insulin resistance.

Importantly, while previous findings relate to non-diabetic individuals and type 2 diabetes patients with preserved insulin secretion, they cannot yet be generalized to patients with impaired insulin secretion. Future physiological studies are needed to elucidate how the intestinal BCAAs and other amino acids enter the bloodstream and from which intestinal location they are absorbed.

Furthermore, new investigations are necessary to know how dietary changes, alone or in combination with microbial or pharmacological interventions, may impact the microbiome and, in particular, influence P. copri modulation of serum BCAA levels: these researches will give a valid sustain on the fight against the pathogenesis of IR and its linked epidemics of common metabolic and cardiovascular disorders (Patterson and Sears 2017; Gopalakrishnan et al. 2018).

Patient involvement in the preoperative setting is crucial. It is important to assist the patient and inform him about the procedure, the achievable goals, and the effects on the life after surgery. For this purposes, many tools can be used by physicians, from dialogue to use of flyers and on-line materials. In fact, when this procedure was applied, it a better patient comfort was observed therefore, in the future, with attention paid to the intervention, patients will tackle, with less disagreement and fatigue, a better predisposition to face the surgery operation with the possibility of mobilizing as soon as possible and perform physical exercises during postoperative period.

Pre-habilitation enables patient undergoing cardiac surgery to face the stress of surgery by augmenting his functional capacity. It decreases sympathetic overreactivity, reduces insulin resistance, and increases the ratio of lean body mass to body fat. Thus, it improves the physical and psychological predisposition to surgery, reducing the complication and the duration of hospital stay, and allows a quick discharge. It is important to follow an educational program, nutritional optimization, exercise training and social support. There is only one limit: these measures evidently may not be feasible in urgent and emergency settings.

Finally, it would be necessary to control alcohol abuse and cigarette smoking, because they increase the risk of many post-operative complications (for example, respiratory, wound, bleeding, metabolic and infective complications). It is proved that smoking interruption and alcohol abstinence for 1 month are associated with improved postoperative outcome after surgery.

Intraoperative Strategies

The personalization of the surgical approach is not simply related to the chosen surgical technique, but must include individualized strategies that allow the optimization of care, the reduction of adverse events and the improvement of the postoperative quality of life.

The administration of antibiotic prophylaxis with cephalosporins 30–60 min before surgical incision, new administration of antibiotics every 4 h (in case the surgery lasts beyond this time frame) and the administration of the antibiotic therapy in the 48 h following surgery plays a fundamental role in reducing surgical site infections. The choice of cephalosporin dosage should be carried out considering the patient's weight (Cimochowski et al. 2001; Edwards et al. 2006; Engelman et al. 2007).

Body temperature monitoring and control is essential in cardiac surgery and hyperthermia should be avoided, especially in the rewarming of patients undergoing cardiopulmonary bypass (CPB). Reaching a central body temperature greater than 37.9°C during rewarming, in fact, has been shown to be associated with renal dysfunction, cognitive deficits and infection (Grocott et al. 2002).

Pain control, once associated only to parenteral opioid administration, should include an opioid-sparing multimodal approach. Opioids, in fact, are associated with multiple side effects including ileus, post-operative nausea and vomiting (PONV), respiratory depression and sedation. High-risk patients can benefit the most from the use of regional anesthesia techniques.

Individual differences in pain sensitivity and patient's response to pain con easily lead to an inappropriate use of opioids, which can cause the onset of side effects.

The research progress on pain-related genes can contribute to personalize the approach and can simplify pain management.

The mu1 opioid receptor gene (OPRM1) appears to be one of the genes implied in the perception of pain and is the most studies opioid target. This gene in fact represents an important target in the treatment of pain because is a binding site for morphine and opioids in general.

In recent years, multiple studies have been carried out that questioned the correlation between OPRM1 A118G single nucleotide polymorphism (which alters transcription of OPRM1 causing an amino acid substitution) and the sensitivity of individuals to pain (Zhang et al. 2019).

Although the effects of OPRM1 A118G gene variant on analgesics requirement remain controversial, OPRM1G allele carriers appears to need a higher mean dose of opioids, when compared to AA (wild-type) homozygotes (Hwang et al. 2014).

The occurrence of PON (post-operative nausea) appears to be reduces in G allele Carriers than in wild-type patients, while there doesn't appear to be any correlation between OPRM1 polymorphism and POV (post-operative vomiting) (Kong et al. 2018).

PONV remains a common occurrence after general anesthesia affecting between 20 and 40% of all surgery patients and with rates of occurrence up to 80% in

high-risk patients and represents one of the major outcomes that negatively affects post-operative satisfaction.

Multimodal approaches to the prevention of PONV have been widely studied and risk factors appears to be female gender, perioperative opioid use, abdominal, ear, throat, nose and breast surgery, use of nitrous oxide and history or PONV or motion sickness. Smoking status seems correlated to a decreased occurrence of this postoperative complication.

The research on the correlation between opioid receptor mu1 A118G polymorphism and the onset of postoperative nausea and vomiting could lead in a near future to a greater personalization of the treatment of this unpleasant event by modifying pharmacological and multimodal approach to PONV treatment and prevention.

The application of the pharmacogenetics findings described above into the clinical practice appears to be premature because other factors like such as age, gender, race and gene-to-gene interactions may influence the outcomes.

Well-designed and large-scale studies are in fact necessary to confirm and validate these preliminary results.

In case of median sternotomy, the execution of a parasternal block guarantees an improvement of pain control of the incision site and seems to reduce the administration of opioid drugs. This would especially benefit those patients who are more sensitive to the adverse effects of opioids.

Acetaminophen (1 g every 8 h) appears to be the safest non-opioid analgesic. When administered together with opioids, it produces a higher level of analgesia and antiemetic effects. Although associated with higher postoperative delirium risk, administration of tramadol can lead to an improvement in postoperative patient comfort and a significant reduction in total morphine consumption (Allen et al. 2017).

For sternal closure, rigid sternal fixation has shown many benefits. It should be recommended especially in high-risk patients, such as those who have already undergone thoracic district radiation therapy, patients on steroids, obese patients and patients with severe chronic obstructive disorder. Rigid sternal fixation appears to be associated with a reduction in wound complications and accelerated sternal healing (Nazerali et al. 2014).

In cardiac surgery—especially in case of surgery that includes extracorporeal circulation (ECC)—the evaluation and management of the patient's coagulation is crucial. Intraoperative anticoagulation is performed by administering unfractionated heparin at a standard dosage, based on the patient's weight. The effectiveness of the dosage administered is evaluated by measuring the activated clotting time (ACT) (Dunning et al. 2008; Foroughi 2018; Pagano et al. 2018).

Bivalirudin can be used as an alternative to heparin, in patients who are resistant or who cannot take heparin (allergic subjects or in case of heparin induced thrombocytopenia) (Gladwell 2002; McNair et al. 2016; Selleng and Selleng 2016).

During surgery, it is necessary to monitor the patient's coagulative aspect, to be able to correct any imbalances and to guarantee effective coagulation when administering protamine sulfate. This is possible through the combined evaluation of the ACT, the number of platelets and their functionality and a careful evaluation of the coagulation factors.

Platelets play a fundamental role in maintaining hemostasis. Any increase or decrease in platelet number and reactivity may increase the risk of bleeding or thrombus formation.

Management of the bleeding and thrombotic events in cardiac surgery appears to be challenging. Bleeding events appears to be more common, but often the treatment of these events is followed by thrombotic events.

The complete evaluation of all the factors that contribute to the formation of an effective and efficient clot is possible through the analysis of a venous blood sample through rotational thromboelastometry (ROTEM) and thromboelastography (TEG). These advanced analyses allow to evaluate the coagulation as a whole process and to discern which of the aspects of coagulation needs optimization and implementation.

There are seven TEG parameters that can be measured. Changes in these parameters usually indicates a pathological coagulability that is more and more severe in relation to the number of TEG parameters that appears to be altered.

The use of tranexamic acid at the maximum recommended dose of 100 mg/kg in patients undergoing cardiac surgery appears to lead to a reduction in the onset of bleeding, and to decrease the risk of tamponade and reoperation in the postoperative period (McNair et al. 2016).

After cardiopulmonary bypass is essential to administer the right dosage of protamine. Excessive dosage can inhibit platelet function and clot formation contributing to the occurrence of postoperative coagulopathy while and inadequate protamine administration can be responsible of bleeding events.

Protamine dosage and titration is decides with the use of one of the two point-of-care (POC) tests: TEG and ACT (Whiting and DiNardo 2014; Bolliger and Tanaka 2017; Emerson and Dabbagh 2018).

Although TEG has been suggested to be a more sensitive indicator of residual heparin than ACT, these two POC appears to be equivalent.

If coagulation is monitored intraoperatively using TEG, TEG-HK (heparinase-kaolin Thromboelastography) R-time difference can be safely used to monitor heparin reversal without the need of ACT (Levin et al. 2014; Petricevic et al. 2015; Deppe et al. 2016; Muñoz et al. 2017; Pretorius et al. 2017; Ahmed et al. 2018; Emerson and Dabbagh 2018).

Transesophageal echocardiography (TEE) plays a fundamental role in the intraoperative phase, as it allows to increase the possibility to perform a tailored surgical and anesthesiology treatment. Its leading role is making the positioning of Swan-Ganz catheter, once widely used in cardiac surgery, no longer one of the principal aids in monitoring patient's hemodynamic set-up in this type of surgery.

In fact, TEE helps the surgeon in the treatment of valvular diseases in the choice of the most appropriate surgical technique, in the evaluation of the effective correction of the treated defect and, in the case of implantation of a valve prosthesis, in the evaluation of the correct implantation of the prosthesis itself. In addition, TEE helps the anesthesiologist in the assessment of residual cardiac function and in gradually weaning the patient from ECC (Desjardins and Cahalan 2009; Akiyama et al. 2013; Buck et al. 2013; Meineri 2016; Muralidhar 2016; Dabbagh et al. 2017).

Reducing surgical incision size has already shown widely studied advantages. Therefore minimally invasive approaches (mini-sternotomy and mini-thoracotomy) should always be preferred to the traditional approach (median sternotomy) in cardiac surgery.

The anatomy of the patient (which must always be widely studied in the preoperative phase), the underlying pathology and the complexity of the surgery must guide the choice among the surgical approaches available. The minimally invasive approach, for example, requires the establishment of ECC by peripheral cannulation. However it may be impossible to perform in case of vasculopathy affecting the limbs in a significant way (Kitamura et al. 1998; Dabbagh et al. 2011; Jha et al. 2014; Balmforth et al. 2017; Paparella et al. 2017; Van Praet et al. 2018; Shahzamani et al. 2019).

Performing valvular surgery may require the replacement of one or more heart valves. Nowadays available on the market are mechanical valvular prostheses and prostheses of biological origin. Patient's age, his life expectancy and lifestyle must steer toward the choice of the best type of prosthetic valve.

Mechanical prostheses guarantee a potentially unlimited postoperative durability but necessarily require the chronic administration of oral anticoagulant therapy (with strict control of INR values). Biological valve prostheses require the administration of anticoagulants only for a short post-implantation period, but have a postoperative durability that varies between 8 and 15 years. Despite the need of reintervention, biological valves are to be recommended and preferred above all in female patients and women of childbearing age. The lack of need of anticoagulant therapy, in fact, reduces the risk of bleeding. The latter could turn out to be deadly, especially during pregnancy and labor.

The current guidelines for surgical treatment of bicuspid aortic valve (BAV) and BAV aortopathy neither differentiate nor personalize the surgical approach. The decision to proceed with proximal aorta replacement (as well as the replacement of the valve) is based solely on aortic diameters, not taking into full consideration the heterogeneity of presentations of the pathology. Personalized methods of assessment—based on non-invasive flow imaging and the measurement of wall shear stress—are currently under examination to implement individualized resection strategies.

Traditional valvular surgical techniques involve the establishment of ECC.

Transcatheter approaches are currently available for patients presenting contraindications to ECC (especially high-risk and elderly patients).

Transcatheter Aortic Valve Implantation (TAVI), TransApical Aortic Valve Implantation (TAAVI) and TransApical Mitral Valve Implantation (TAMVI) do not require the aid of extracorporeal circulation for the implantation of cardiac valve prostheses (Brennan et al. 2013; Kaneko et al. 2014; Nishimura et al. 2014; Hiratzka et al. 2016; Kanhere and Kanhere 2016; Sundt et al. 2016; Goldstone et al. 2017; Andersen and Turek 2018; Bollache et al. 2018).

Personalizing the anesthetic procedures in patients undergoing heart surgery means above all monitoring the patient.

Tailored intraoperative anesthesiology conduct should be grounded on a careful examination of the real clinical conditions of the patient—and of the evolutions and changes of these conditions during surgery—and a complete analysis of the patient himself. The depth of the hypnosis level should be verified and corrected on the basis of bispectral index (BIS) or electroencephalography (EEG).

The use of Near Infrared Spectroscopy (NIRS) and Transcranial Doppler (TCD) sonography find significant reflection in neuromonitoring, especially in the case of high-risk patients or surgical procedures that require circulatory arrest.

TCD is a bedside technique that allows visualization of cerebral blood flow and the evaluation of cerebral perfusion and vaso-reactivity, providing instant feedback.

It consents changes in strategy and a strict monitoring of treatment response (Saidi and Murkin 2005; Kertai et al. 2012; Kampf et al. 2013; Berger et al. 2014; Nitzschke et al. 2014; Bevan 2015; Ghazy et al. 2016; Chan et al. 2017; Dabbagh 2018a, b; Fani et al. 2018; Lewis et al. 2018; Totonchi et al. 2018; Yu et al. 2018).

In congenital heart defects' surgery, increasing interest and studies are focusing on the possibility of using the aid of new imaging technologies and 3D-printed models. The creation of three-dimensional models customized on the imaging studies allows to simulate the surgery improving the programming of the surgery itself. Therefore these new technologies could be helpful in treating high-risk patients and in the most difficult surgical procedures (Valverde 2017; Valverde et al. 2017; Sun et al. 2019).

Postoperative Strategies

Perioperative Glycemic Control

The glycemic intra-operative and post-operative control allows to improve surgery outcomes. It is necessary to avoid hyperglycemia because it may cause damages through oxidative stress, prothrombotic and inflammation effects. It is demonstrated that a preoperative carbohydrate loading decreases glucose levels after abdominal and cardiac surgery. The control on level of glucose in the blood is fundamental to avoid the risk of toxicity.

Moreover, it must be considered that epidural analgesia during cardiac surgery reduces hyperglycemia incidence. It is necessary to treat the level of glucose when this is higher than 160–180 mg/dl: the treatment can be made with an insulin infusion for the patient undergoing cardiac surgery, so as to maintain an optimal glycemic value.

Pain Management

Today, about 30–80% of patients undergoing cardiac surgery experiment acute postoperative pain. Pain affects the reaction of body to surgical stress, altering many homeostatic systems, such as cardiovascular system, immunologic system (involved

in inflammatory response) and neuroendocrine system. The result is an increased risk of postoperative complications and mortality. An optimal control of pain is a goal of "heart team" in order to achieve a better satisfaction and less patient discomfort and to decrease length of stay: in addition, this would decrease costs.

First of all, after cardiac surgery the precise cause of acute postoperative pain must be determined. The first diagnosis to rule out is an underlying residual ischemia or incomplete revascularization. Other common causes of postoperative pain are: pain deriving from myofascial and/or thoracic wall including muscles, bones, tendons and ligaments, site of incision of sternotomy or thoracotomy, intraoperative tissue retraction and surgical dissection, the arterial and venous vascular cannulation sites, the site of vein harvesting, the chest and abdominal sites for chest tubes.

The American Society of Anesthesiologists' Practice Guideline for Acute Pain Management in the perioperative setting defines "pain management in the perioperative setting" as the "actions before, during, and after a procedure that are to reduce or eliminated postoperative pain before discharge" (American Society of Anesthesiologists Task Force on Acute Pain Management 2012).

There are many techniques available to manage postoperative pain. First to mention is the traditional intravenous administration of analgesics, especially opioid analgesia. Opioids may influence homeostasis including the hypothalamus-pituitary-adrenal (HPA) axis and the extrahypothalamic brain stress, and may control immunomodulation. Unfortunately, opioids, in particular morphine, decreases the mobility of ileo and GI tract ending not only in constipation and, sometimes, also aggravate centrally mediated nausea and vomiting. In addition, they are associated with adverse effects including nausea, vomiting, pruritus, urinary retention, respiratory depression and delayed tracheal extubation.

Therefore, from new diagnostic evidences, multimodal opioid sparing approaches can protect against pain through the additive or synergistic effects of other different drugs, allowing lower opioid doses.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs) have analgesic and anti-inflammatory properties, through the blockade of cyclooxygenase enzyme, leading to prostaglandin synthesis inhibition. Even if selective COX-2 inhibitors decrease the unwanted effects of nonselective inhibition of COX-1, especially regarding the GI mucosa, the most important adverse effects of NSAIDs are:

- Gastrointestinal hemorrhage, condition that worsens by concomitant administration of anticoagulant
- Increased risk of bleeding which could be a contraindication for neuraxial block for control postoperative pain
- Acute renal ischemia, if associated simultaneous with diuretics, angiotensin-converting enzyme inhibitors "ACE inhibitors", and/ or angiotensin receptor antagonist "ARA"

Thus, NSAIDs, as adjuvant, could reduce opioids dose during the postoperative period without complications if prescribed according to the optimal dose range in order to avoid their contraindications.

Paracetamol (N-acetyl-p-aminophenol) is one of many analgesics that can be used as opioid adjuvant. Even though it has been proved to be the safest analgesic,

nowadays the complete mechanism of paracetamol is not well known; its main toxicity is hepatotoxicity when large doses are swallowed (the optimal dose of paracetamol is 1 g every 8 h in a contest of a multimodal analgesic regimen).

N-acetyl-p-aminophenol reduces opioid dose required for postoperative pain control and has an independent effect against postoperative nausea and vomiting.

In fact, a randomized controlled trial demonstrated that the administration of intravenous acetaminophen during cardiac surgery and for the first 24 h postoperatively reduced opioid consumption, improved patient satisfaction with their overall pain experience but did not reduce opioid side effects.

Tramadol has both an opioid—and a non-opioid effect, and allows to decrease by 25% morphine use, with an optimal pain control: it also increases the wellbeing of patients during postoperative time.

Pregabalin and gabapentin have been used for acute pain treatment with reducing opioid dose in a multimodal strategy. Their mechanism of action is inhibition of glutamate release through NMDA antagonism. Pregabalin administration 1 h before surgery and for two postoperative days guarantees better pain control compared with placebo. A 600-mg gabapentin dose, 2 h before undergoing cardiac surgery, reduces pain exacerbation, allows opioid sparing, and lowers postoperative nausea and vomiting.

Other useful drugs are alfa2-adrenergic agonists, dexmedetomidine and clonidine for example, which guarantee analgesia, sedation and sympatholysis. Alfa2-adrenergic agonists, when used as sedative after cardiac surgery, have the following desirable effects:

- Increased stability of hemodynamic parameters and reduced hemodynamic responses
- Cardiac protection
- Decreased use of opioids
- Antiarrhythmic effects
- Protection from delirium

Finally, other pain control techniques can be used as wound infiltration with local anesthetics, intercostal nerve block, parasternal block, intra-pleural infiltration with local anesthetics, and neuraxial analgesia.

Therefore, the heart team must indicate a pain control strategy and an opportune monitoring pain scale to improve comfort of patient. The Critical Care Pain Observation Tool, Behavioral Pain Scale, and Bispectral Index monitoring may have a role in this setting (Bigeleisen and Goehner 2015; Wick et al. 2017; Bignami et al. 2018; Kumar et al. 2018; Yu et al. 2019).

Postoperative Systematic Delirium Screening

Delirium is defined, according to the DSM-5 (Diagnostic and Statistical Manuel of Mental Disorders, Fifth Edition), as “a neurocognitive disorder or neuropsychiatric syndrome with its hallmark as disturbed attention and awareness developing over a

short period of time". Postoperative delirium after cardiac surgery occurs in about 50% of the cases; unfortunately, sometimes this condition is misdiagnosed or underdiagnosed.

Risk factors for delirium are: pre-existing dementia, history of hypertension, history of alcoholism, high severity of illness at admission. At last, coma is an independent risk factor for development of delirium in Intensive Care Unit patients.

Many times, early identification of postoperative delirium can help to recognize the underlying condition (pain, hypoxemia, low cardiac output and sepsis, for example) in order to begin appropriate treatment as soon as possible. Many are the instruments for Delirium screening that could be used as the Confusion Assessment Method for the Intensive Care Unit or the Intensive Care Unit Delirium Screening Checklist. The principle strategy for prevention and treatment of delirium is mainly a no pharmacology approach, which includes compensation or prevention of sleep deprivation, intervention for improved patient comfort, exercises with physical therapy, and, if necessary, intervention for avoidance of social isolation.

There is no scientific evidence that a pharmacology approach (the use haloperidol or atypical antipsychotics, for example) has an impact on delirium prevention.

Persistent Hypothermia

Postoperative hypothermia is defined as the failure to maintain normothermia (>36 °C) for 2–5 h after surgery. A transient hypothermia after cardiac surgery is very common and not associated with increased mortality, while a persistent hypothermia determines higher risk of bleeding, infection and hospital mortality. Therefore, it is very important to avoid postoperative hypothermia by using forced-air warming blanket, raising the ambient room temperature, and warming irrigation and intravenous fluids.

Chest Tube Patency

Bleeding is a common problem after cardiac surgery, and can result in tamponade or hemo-thorax. Thus, a pericardial drain is always necessary to evacuate shed mediastinal blood. It has been demonstrated that these drains tend to be clogged, causing collection of fluids around heart or lung: this is the situation leading to pleural or pericardial effusion, triggering postoperative arrhythmias, hemodynamic problems and other complications.

At the moment, many strategies are implemented to maintain tube patency as stripping and milking, but according to a recent meta-analysis this technique is ineffective and potentially harmful. Another technique is based on the positioning of a smaller tube in the bigger one for clot suction, but this may be dangerous because it can increase risk of infection and of internal structure damage.

Five non-randomized clinical trials suggest the use of an active chest-tube clearance method to guarantee tube patency with better results: in addition, this method reduces postoperative atrial fibrillation, suggesting that retained blood may be a trigger for this common problem.

The timing to remove the mediastinal drain is not standard yet; on the other hand, evidence suggests to start the drain removal with safety when drainage becomes macroscopically serious.

Chemical Thrombo-Prophylaxis

Thrombotic events, including both deep venous thrombosis and pulmonary embolism, are very common during post-operative period after cardiac surgery. Prevention of this complication is central in the perioperative period. The use of mechanical thrombo-prophylaxis with compression stockings and/or intermittent pneumatic compression during hospitalization, until the patients are adequately mobile, reduces the risk of thrombo-embolic events.

Prophylactic anticoagulation must be administered from first day post-surgery, or at least as soon as satisfactory hemostasis has been achieved (Koster et al. 2015).

Extubation Strategy

A longer period under mechanical ventilation after cardiac surgery is associated with higher morbidity and mortality because of ventilator associated pneumonia and significant dysphagia.

Early extubation, within 6 h of Intensive Care Unite arrival, is obtained with time-directed extubation protocols and low-dose opioid anesthesia, reducing ICU time, hospitalization period, and relative cost.

Kidney Stress and Acute Kidney Injury

Acute Kidney Injury (AKI) is a major complication that occurs in 22–36% of patients undergoing cardiac surgery, so relevant that 1–6.5% of these patients require renal replacement therapy (RRT). AKI is an independent factor of risk of mortality (up to 60% when severe) and represents an almost eightfold increased risk for the development of chronic kidney disease (CKD).

The pathogenesis of AKI in cardiac surgery is very complex.

Nephrotoxic exposure can be caused by drugs such as antibiotics (beta-lactams, vancomycin, or aminoglycosides that can cause acute interstitial nephritis or direct injury); angiotensin-converting enzyme inhibitors, which inhibit renal efferent

arteriolar vasoconstriction; free hemoglobin (Hb) is another potential nephrotoxic thought to contribute to AKI in patients after cardiac surgery.

Many factors work together as nephrotoxic: together with drugs, ischemia and ischemia-reperfusion injury, athero-embolism, exposure to cardiopulmonary bypass and activation of inflammatory pathway must be cited among them.

For this reason, it becomes important to find early markers that allow to identify patients with risks of renal damage in order to quickly apply therapeutic strategies to reduce the incidence of kidney injury.

Two novel biomarker for AKI have been identified and can be added to classical biochemical exams. In fact, urine levels of TIMP-2 and IGFBP7 are predictive for AKI at an early time point (1 h after starting Cardiopulmonary Bypass), for example.

A therapeutic approach establishes the fundamental elements: avoiding nephrotoxic agents, breaking off angiotensin converting enzyme inhibitors and angiotensin II antagonist for 48 h, close monitoring of creatinine and urine output, avoiding hyperglycemia and radiocontrast agents, close monitoring to optimize volume status and hemodynamic parameters.

Although many risk scores for AKI after Cardiac surgery are well known, they are considered optimal discrimination in assessing low-risk patients but relatively poor in assessing moderate—to high-risk patients. Therefore, it is clear that it is necessary to work on these prevention procedures (Agrò et al. 2018a, b).

Goal-Directed Fluid Therapy (GDT)

In cardiac surgery, a rational fluid administration is a required tool to optimize tissue perfusion, avoiding hypo- and hypervolemia in those cases of reduced tolerance.

Goal-Directed Fluid Therapy (GDT) is an articulate strategy for fluid infusions in respect of tissue perfusion and oxygenation. Through hemodynamic monitoring, physicians can administer fluids according to GDT, and inotropic or vasoactive drugs, only to patients who need them. This is crucial to grant the metabolic requirement. So, applying GDT, hemodynamic management is different in every single patient, with high grades of personalization.

A correct approach in GDT is based on the prediction of fluid responsiveness. Fluid-responder patients are those who, according to Starling's law, will benefit from fluid loading in terms of hemodynamic stability and DO_2.

It is demonstrated that if fluid responsiveness is not evaluated, only 40–72% of critically ill patients respond to GDT with a significant increase in stroke volume.

Targets of GDT are represented by filling pressures, such as central venous pressure CVP, mean arterial pressure MAP, and Pulmonary capillary wedge pressure PCWP; those pressures are used to guide intravascular volume therapy. In cardiac ICU, CVP is the most used (87% of intensivists), followed by MAP (84%) and PCWP (30%).

Other hemodynamic targets are stroke volume variation (SVV), pulse pressure variation (PPV) and continuous CI, which can be obtained from pulse wave analysis

thought intermittent transpulmonary thermodilution. Finally, volumetric parameters to be considered are the Global end-diastolic volume (GEDV), and intrathoracic blood volume (ITBV).

Under some specific circumstances, as left ventricular failure or acute lung injury, the EVLW (extravascular lung water, index of lung edema) can be used. EVLW is an independent predictor of survival. At last, left ventricular end-diastolic area (LVEDA), the most popular echocardiographic parameter used to assess preload, is a valid parameter to guide fluid management in cardiac surgery patient and to evaluate fluid responsiveness.

A hemodynamic assessment and monitoring plays a central role in control of GDT. This can be achieved thanks to systems such as Swan-Ganz or pulmonary artery catheter (PAC) that are the gold standard, despite their invasiveness. In fact, these systems can expose patient to complications, and cannot be used without adequate training and experience.

New monitoring devices, evaluating dynamic and volumetric parameters, are PiCCO system and PiCCO2, Flotrac Edwards Life systems and LiDCOrapid.

These devices use transpulmonary thermodilution and/or pulse wave analysis and require invasive arterial lines and a central venous catheter. However, they are less invasive than PAC.

Volume responsiveness is not the only parameter of GDT, but also responsiveness to vasoconstrictor and inotropic agent should be considered: the only goal of therapy is hemodynamic stability.

GDT has been demonstrated to reduce length of ICU stay, improving outcomes. Goal directed fluid therapy trials consistently demonstrate reduced complication rates and length of stay in surgery overall and specifically in cardiac surgery (Raghunathan et al. 2013; Della Rocca et al. 2014; Kampmeier et al. 2014; Dabbagh 2018c; Rehm et al. 2019; Silversides et al. 2019).

Conclusions

The personalization of medical care represents one of the most important challenges for modern medicine.

Tailored treatments could offer significant advantages for patients by reducing the occurrence of complications, improving outcomes and quality of life.

Even in cardiac surgery it is possible to personalize clinical and surgical approach to the patient, even if much work remains to be done.

The implementation of new technologies allows a close monitoring and control of what happens during surgery, allowing the implementation of strategies aimed to improve the conditions of the patient.

3D printing technology, although still requiring large scale validation studies and with the limitations still linked to production's costs of three-dimensional models, proves to be promising in elective treatment of cardiac and vascular malformations

and represents one of the most innovative fields of research in the personalized approach to heart disease.

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Chapter 5
Personalized Anesthesia for Lungs and Respiratory Tract

Ata Mahmoodpoor

Respiratory Tract and Anesthesia Related Interactions

Despite low anesthesia-specific risk, anesthesia management has important impacts on perioperative risk and perioperative outcomes. The adverse perioperative events which remain frequent, and occur in about 30% of hospital admissions, may be preventable in more than 50% of the cases, and show increasing trends according to current research results. The preoperative assessment of patients' pulmonary function is an essential part of preoperative evaluation having significant effect on decreasing post-operative pulmonary complications. This complication may be due to different pre-existing comorbidities, techniques and drugs used for anesthesia and surgical pathology (Bevacqua 2015). Patient safety should target avoidable patient harm and should be assessed, irrespective of the discipline, as carefully as any other healthcare intervention regarding their effectiveness, potential direct and indirect undesired effects, and cost-effectiveness. The NAPT study in UK showed that airway management was poorly judged in almost 3/4 of cases which can affect patient outcome (Cook et al. 2011). Each anesthetist should have a plan B besides proven technologies like fiberoptic bronchoscopy, capnography, LMA, and etc. for possible difficult airway situations. Inside the operating room, 67% of difficult intubations are noted at induction of general anesthesia, and may occur in individuals who were originally assessed as having a "normal airway". Anesthesiologists caring for the patients should also evaluate their patients regarding respiratory complications and possible risk factors. There are many scores for the prediction of respiratory complications and ARDS. The Lung Injury Prediction (LIP) Score is an alternative model initially developed for all patients, and validated in surgical critical care patients. Also, early oxygen

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saturation to fraction of inspired oxygen ratio (within 6 h of hospital admission) has been shown to be an independent indicator of ARDS development in patients at risk (Kor et al. 2014; Festic et al. 2015).

On the other way, early recognition of underlying respiratory problems and identification of causative pathogens are essential parts of preoperative management. Preoperative bedside lung ultrasound may offer additional diagnostic information about possible respiratory complications (Bass et al. 2015). Also routine approaches to reduce gastric aspiration and ventilator-associated pneumonia should be employed.

Traditional Solutions

Preoperative evaluation of each patient should be performed based on these findings: history and physical examination, previous exposure to pulmonary toxic drugs, tobacco use, airway and cardiovascular examination, diagnostic and laboratory tests like: chest X Ray, chest CT and MRI, spirometry, blood testing, carboxyhemoglobin, kidney function, arterial blood gas analysis, and exercise testing to reach the comorbid pulmonary disease (Scholes et al. 2009). Previous studies showed that there was a higher risk of pulmonary complications for patients who had a history of upper respiratory tract infection during the preoperative period, patients who underwent cardiac surgery, patients who had shortness of breath, a history of COPD, and a RI infiltration in the chest X-ray. These parameters should be examined carefully in the preoperative period, and physicians should be careful in terms of pulmonary complications that may develop during the postoperative period. There are some risk prediction scores but it is often difficult to balance these prediction scores with clinical status of the patients in the real life experience, which can lead to misprediction of the patients' status and postoperative complications (Johnson et al. 2017). Previous studies showed that checklists, team work and communication in operating room and compliance with safety measures, could decrease all perioperative anesthesia-related complications (Wacker and Staender 2014). Each anesthesiologist should be familiar to the difficult airway algorithm. Also surgical airway should be taken into consideration early in the event of a 'can't ventilate can't intubate' scenario and requires active communication between the anesthesiologists and the surgeons. From a pharmacological standpoint, the introduction of sugammadex for reversal of neuromuscular blockades may become an adjunct to the difficult airway algorithm. Sugammadex actively binds to rocuronium or vecuronium, eliminating the paralysis induced by those agents. Although it has been used in the clinical event of inability to intubate, its usefulness for 'can't intubate can't ventilate' has been called into question due to the time it takes to draw up, administer, circulate and have an effect (Steadman et al. 2017).

Personalized Medicine Solution

The concept of "one size fit all" does not work well for medical therapies nowadays. For many years the aim of physicians has been to provide an effective treatment and predict an appropriate outcome for their treatment. But in practice patients showed different responses for a single or combination of drugs (Cesuroglu et al. 2016). The solution for preventing these ineffective treatments, serious adverse effects, different morbidities and mortality can lie in the emerging field of personalized medicine. Personalized medicine is the concept of tailoring pharmacotherapy to an individual patient based on their predicted response to that therapy. Its application to perioperative medicine is novel, and has a great potential for growth. Despite recent advances in the field of personalized medicine, this approach has not yet been widely developed in the preoperative medicine. But personalized medicine can play an important role in the preoperative period (Ginsburg and Phillips 2018). General anesthesia is a state of unconsciousness, amnesia, analgesia and akinesia induced with some drugs like opioids, muscle relaxants, hypnotic/sedative agents and antiemetics. Clinical and genetic factors like patient's age, ethnicity, genetic mutation and comorbidities can change the efficacy of these drugs. Much progress has been made in omics research following the completion of the Human Genome Project. This comprehensive analysis introduced the bioinformatics which is contributed to the clinical practice of anesthesiology. Patients' genomes show genetic variations and may predict the sensitivity to anesthetics and analgesics, incidence of adverse effects, and intensity of postsurgical pain. In addition, novel epigenome researches may explain why environments change the phenotypes of clinical anesthesia.

Genomics/Pharmacogenomics

The preoperative period represents a good example of using personalized medicine in our practice in both operating room and intensive care unit. There is interindividual variability in patients' response to different stresses like hemodynamic changes, surgical injury, vascular cannulation, extracorporeal circulation, intraaortic balloon counterpulsation, mechanical ventilation, organ resection and donation, transfusion and anesthetic agents (Saba et al. 2017a, b). For many years we thought that this variability is related to different parameters like age, nutritional status, comorbidities and etc. We now know that genomic variation contributes to most of these differences in patients' response. Pharmacogenomics focuses on identifying genetic variants which modulate pharmacokinetic and pharmakodynamic of the drugs. The earliest report of pharmacogenomics goes back to 510 BC, Pythagoras reported the development of hemolytic anemia in patients who ate fava bean, which is now related to G6PD deficiency (Relling and Evans 2015). In 1950, Friedrich

Table 5.1 Important considerations related to successful clinical implementation of pharmacogenomics

Clinical scenario	Computer technology	Socioeconomics
Evaluation of effectiveness	Storage of pharmacogenomics data	Cost
Valid therapeutic targets	Electronic health record integration	Reimbursement
Improvement of assays	Thoughtful software design	Physician use
		Education
		Ethics

Vogel used the term "pharmacogenetics" for the first time (Relling and Evans 2015). With increasing evidence from literature, genomic variations can significantly modulate the risk of anesthesia and operative related anesthesia, so preoperative genomics provides innovative functional approaches and techniques to define the individualized responses to anesthesia and operation (Linares et al. 2014, 2015). Hence preoperative genomics has gained good results but its implementation in clinical practice is very slow. To solve this problem we need more evidence from high quality clinical studies for preoperative genomics, newer point of care techniques and easy to access methods for patient care and settings to adjust it to regular clinical practice (Gabriel et al. 2017). Genomic study should be started in surgeons' clinic or anesthesia clinic prior to the scheduled surgery, so healthcare providers can modulate the potential genetic risks to specific drugs. Based on recent studies, implementation of this technique to ERAS protocols will further facilitate more widespread adoption (Helander et al. 2017; Modesitt et al. 2016). Important considerations related to successful clinical implementation of pharmacogenomics were shown in Table 5.1.

Prolonged Apnea After Succinylcholine Administration

Dr. Werenr Kalow introduced pseudocholine esterase deficiency for the first time (Jones 2011). After that he developed a method to detect the so called "atypical pseudocholine esterase" activity by dibucaine among normal variants, heterozygotes, and homozygotes, which remains the standard of detection of this disease today (Kalow and Genest 1957). Nowadays we are aware of at least 10 different polymorphisms of pseudocholine esterase with K and A variants as the most common types. The K type leads to decreased production of the enzyme but the A type results in the dibucaine-resistant version (La Du et al. 1990).

Malignant Hyperthermia

The exact mechanism of malignant hyperthermia (MH) is still unknown. Muscle rigidity after succinylcholine is an early warning sign which may suggest a skeletal muscle abnormality. A mutation in ryanodine receptor was proposed as a mediator

for malignant hyperthermia (MacLennan et al. 1990). Now we know more than 200 ryanodine gene variants which only about 20 are considered to influence the patients' susceptibility to MH (Davis and Brandom 2009).

Opioid Analgesics Metabolized by CYP2D6

Codeine is a prodrug which is metabolized into morphine by CYP2D6. Some patients who have two dysfunctional copies of this gene are unlikely to convert codeine into morphine and therefore are unlikely to achieve analgesic effects. Some patients have two functional copies of the gene which are able to completely metabolize codeine (Palmer et al. 2005). These individuals are at increased risk of respiratory dysfunction after anesthesia even after standard doses of codeine. If an individual is known to be an ultra-rapid metabolizer, opioid drugs which rely on CYP2D6 like codeine, tramadol, hydrocodone and oxycodone are not recommended for analgesia and other drugs that their metabolism is not dependent on CYP2D6, like morphine or nonopioid analgesics should be considered (CPIC n.d.). It seems that ethnicity has a great impact on the incidence of the CYP2D6 polymorphism, as Ethiopians, Arabs, North Africans have nearly a 30% incidence of ultra-rapid metabolizer gene (Mizutani 2003).

Nitrous Oxide Toxicity

Prolong exposure to N_2O can be associated with megaloblastic anemia, agranulocytosis and neuropathy. Neuropathy can be seen with short-term exposure to N_2O in children with variants in the gene encoding 5,10 methylene tetrahydrofolte reductase (MTHFR). So, N_2O should not be administered to patients with MTHFR deficiency or a familial history of this condition. Previous studies showed raised plasma homocysteine concentrations after 2 h nitrous oxide exposure in patients homozygous for either of the two common variants in the MTHFR gene (Selzer et al. 2003). The clinical importance of these observations is not known, but if transiently increased plasma homocysteine concentrations is shown to be associated with worse clinical outcomes, physicians should check genotyping of MTHFR variants preoperatively to perform safe personalized anesthesia (Hogan 2008).

Intraoperative Respiratory Complications

Anesthesia has several respiratory complications which should be considered during the operation. Some of these complications are atelectasis due to reduced functional residual capacity, high Fio_2 and positioning, increasing closing volume and decreasing minute ventilation and increased alveolar dead space ventilation.

Traditionally anesthesiologists try to reduce these complications by applying positive end expiratory pressure, higher respiratory rate with low tidal volume strategy, recruitment maneuvers, optimized use of neuromuscular blocking drugs with monitoring the depth of block, and head elevation during the intraoperative period. Following we describe pharmacogenetics of some drugs that are used during anesthesia and it seems logical that having information on patients before surgery would be a valuable tool to anesthesiologists because it can allow effective and ideal management of anesthesia in each patient. Different drugs used during anesthesia may have different effects on respiratory function based on genetic variations as the followings:

Morphine

Is frequently used during anesthesia for acute and chronic pain control. OPRM1 is an important gene in pharmacogenetic properties of morphine. Previous studies showed that patients with OPRM1 rs 1,799,971 variation had the lowest morphine consumption and pain scores but a high incidence of nausea (Sia et al. 2008). Previous studies showed that patients with ABCB1 rs 1,128,503 and rs 1,045,642T alleles required less morphine for acute postoperative pain control (Bastami et al. 2014). Also mutation of ABCB1 rs 9,282,564 gene can result in respiratory depression with morphine (Sadhasivam et al. 2015).

Finally, due to the small effect size and unconfined reproducible outcomes of the current studies, OPRM1 and ABCB1 may not serve as an ideal predictive biomarkers and more strong evidences are required to guide morphine use in the clinic, based on a patient's genetic profile (Stamer et al. 2013a).

Codeine

Based on the 2014 CPIC guidelines for cytochrome P450 2D6 genotype and codeine therapy, *CYP2D6* extensive metabolizers and intermediate metabolizers could use label-recommended dosing but ultra-rapid metabolizers and poor metabolizers are recommended to use alternative analgesics rather than codeine (Crews et al. 2014).

Fentanyl

*CYP3A5*1* is the only functional allele, individuals with at least one **1* allele are expressers while others are nonexpressors (Tanaka et al. 2014) but those patients who had rs2076222 C allele showed lower sensitivity to fentanyl (Mieda et al. 2016). So knowing this information help physicians to decrease respiratory complications.

Tramadol

Tramadol is metabolized by CYP2D6 to its main active metabolite O-desmethyltramadol and current guidelines recommend that ultra-rapid metabolizers should either reduce the dose by 30% or use another drug. Intermediate metabolizers should be aware of reduced efficacy and resistant individuals should use alternate drugs. Although these clinical therapeutic recommendations cannot achieve personalized precision medicine at present, the utility of *CYP2D6* genotype to tramadol dosing is certain (Dean 2015).

Oxycodone

Oxycodone can treat multiple types of pain and is often a substitute for other opioids when they are ineffective. The recommendations for oxycodone are similar to the guideline for tramadol and codeine, so the alternative drug should not contain tramadol or codeine which is metabolized by CYP2D6 (Stamer et al. 2013b).

Methadone

Methadone is generally used in addicted patients and recent studies showed that CYP2B6 can be a key dose-guiding element regarding its effect on different individuals (Yang et al. 2016).

Aspirin

Differences in *UGT1A6* and *CYP2C9* have been implicated in aspirin resistance and the safety of antiplatelet doses. Also other genes such as *GP6* and *PEAR1* were studied more extensively in relation to this function (Yiannakopoulou 2013).

Ibuprofen

Recent studies have shown that CYP2C8*39 (increased metabolism of *R*-ibuprofen), CYP2C9*2 and CYP2C9*3 (decreased clearance of ibuprofen) are important alleles in the metabolism of ibuprofen and all these alleles lead to a reduced activity of CYP enzymes (López-Rodríguez et al. 2008).

Barbiturates

More evidence is needed to elucidate the mechanism of this drug and the genes that may influence its efficacy however these drugs are largely replaced by benzodiazepines.

Midazolam/Diazepam

Midazolam is metabolized by CYP3A in liver and the results of a study in 24 Asian patients with advanced stage gastrointestinal cancer showed that *CYP3A5*3* carriers had 22% lower typical clearance of midazolam than noncarriers. Also, *CYP3A4*22* T allele was associated with reduced oral clearance of midazolam in non-*CYP3A5*3* carriers (De Jonge et al. 2015). Choy et al. in their study showed that polymorphism of rs4263535 (187 + 3553A > G) in *GABRA1* intron 4 was associated with more sedation induced by midazolam and patients with rs4263535 required a less dose of midazolam (Choi et al. 2015).

Previous studies showed that CYP2C19 polymorphism can affect diazepam pharmacokinetic. But a newly performed study in south Indians showed no significant correlation between CYP2C19 and diazepam kinetic (Jose et al. 2016).

Propofol

Propofol is metabolized by CYP2B6 in the liver, but nearly 70% of propofol undergoes *O*-glucuronidation by UGT1A9 (Mikstacki et al. 2013a). However, both SNPs of CYP2B6 and UGT1A9 showed no significant effects related to propofol metabolism in a previous study (Loryan et al. 2012), so we need more evidence to show the exact effect of these variations in the kinetic of propofol.

Volatile Anesthetics

CYP2E1 plays an important role in the metabolism of these agents and also other genes such as *MC1R* are also related with the anesthetic effect of volatile anesthetics (Mikstacki et al. 2013b). Different studies showed that the serum α-GST can be used as a marker of hepatic condition, especially for sevoflurane (Cohen et al. 2012).

Dexmedetomidine

Although data regarding the metabolism of dexmedetomidine is limited, an important route of metabolism is mediated essentially by CYP2A6 (Kohli et al. 2012). But a few studies showed that patients with *ADRA2A* rs1800544 (-1291C > G) G allele had higher Bispectral Index and Ramsay Sedation Scores indicating a prolonged time to falling asleep; this should be considered when using this drug as a sedative (Yağar et al. 2011).

Neuromuscular Blocking Agents

Succinylcholine is hydrolyzed by BChE in plasma; based on previous trials, *BCHE*FS126* can silence the enzyme function and cause prolonged duration of neuromuscular blockade (Delacour et al. 2014).Also, seven novel mutations were found in *BCHE* (I373T, G467S, W518R, L184S, V421A, M462I and R577H) that were associated with prolonged effect of succinylcholine or mivacurium (Wichmann et al. 2016).

Antiemetics

Postoperative nausea and vomiting (PONV) is one of the most common complications in clinical anesthesia, and receptors such as dopamine, opioid and 5-HT3 receptors are related to the emetic center. The CPIC guideline published in 2016 summarized that patients with *CYP2D6* UM are recommended to select an alternative drug to ondansetron, which is not predominantly metabolized by CYP2D6 (Bell et al. 2017). Previous studies showed that polymorphisms of *ABCB1* can affect the expression and function of P-gp which are associated with ondansetron efficacy (He et al. 2014), but more recent studies showed that *ABCB1* might not serve as a suitable predictive biomarker in drug treatment (Bruhn and Cascorbi 2014). *SLCO1B1*, *ABCB1* and *CHRNA1* gene polymorphisms in Chinese patients combined with ondansetron administration, *ABCB1* rs1128503 TT, and *SLCO1B1* rs2306283 (A388G) AG/GG patients, were shown to have a prolonged clinical duration and recovery time (Mei et al. 2015). Like ondansetron, the *CYP2D6* genotype is significantly associated with the effects of tropisetron and this genetic factor should be considered with regards to the dosage of tropisetron, as recommended by the CPIC guideline (Bell et al. 2017).

Vasopressors

Zhang et al. showed that the EDN2 gene has a strong biological relevance to vasoconstriction by binding to endothelin type A receptors on arterial smooth muscle cells but we need further trials to show the clinical effectiveness and the importance of this finding (Zhang et al. 2019).

Pharmacogenetic studies of anesthetic drugs will help physicians to understand their genetic contribution and to decrease their complications. On the other hand, the different results because of the heterogeneous and small sample sizes of these trials, makes the implementation of pharmacogenetics difficult in the field of anesthesia.

Personalized Medicine in Interstitial Lung Disease

During the past years molecular and genetic approaches regarding diagnosis and management of interstitial lung disease (ILD) improved dramatically. The importance of personalized medicine in ILD should be established and more projects are needed to prospectively validate the available data. One could argue that the cost of personalized in ILD could be very high, especially in times when research resources are limited. However, the validation and use of reliable peripheral blood biomarkers in ILD could counterbalance this argument, with a substantial potential for reduction in healthcare cost by decreasing the number of lung biopsies for diagnosis and CT scans for disease progression monitoring and also a decrease in ICU length of stay. Before implementation of precision medicine we should answer these questions: identify unmet need, define intended use population, biomarker discovery, analytical validation, clinical validation, Establish broad clinical utility and enable widespread use.

Interstitial Pulmonary Fibrosis

Although environmental risk factors have long been known in IPF, genetic risk factors have recently been established. Regarding heterogeneity in IPF natural history, a genome wide investigation aimed at identifying single nucleotide polymorphism linked to IPF prognosis would greatly increase our ability to incorporate genetics into prognostic scores, diagnostic and therapeutic models (Herazo-Maya et al. 2013).

Sarcoidosis

Because of the lack of diagnostic gold standard for sarcoidosis, lack of standard protocol for management, highly variable mode of presentation and poor correlation between disease activity and severity development and applicability of biomarkers remains problematic.

Pulmonary Hypertension

Recent trials have shown the application of molecular phenotyping in diagnosis and management of PAH (Sweatt et al. 2019a). We should intend to expand the cytokine and chemokine panel, broadly assess the circulating immune cell landscape, examine transcriptomic profiles to ascertain differentially expressed transcripts and enriched biological pathways, and analyze histopathology in explanted lungs from transplant recipients (Hollander et al. 2017). In the future invention of point-of-care test that feasibly stratifies immune endotypes and guides the selection of precision immune-targeting therapies will help to management of this disease. Application of machine learning algorithms to these types of datasets will allow physicians to be exemplars of an optimal system that is facile enough to be utilized for prevention, diagnostics, or therapeutics. This evolving use of precision medicine to understand and define subphenotypes of patients with pulmonary hypertension, therefore, has the potential to improve health, support prevention strategies, and select interventions with a high probability of successful outcome (Sweatt et al. 2019b).

Personalized Medicine for Chronic Obstructive Lung Disease and Asthma

Nonresponse to pharmacologic and non-pharmacologic treatments is common, and many patients have refractory symptoms. Thus, there is an ongoing urgency for a more targeted and holistic management of the disease, incorporating the basic principles of P4 medicine (predictive, preventive, personalized, and participatory). Currently Strategies to personalize the treatment of exacerbations are not available but increased understanding of individual genetic variants modulating the immune response involved in exacerbation susceptibility and response to therapy may improve personalized exacerbation management in future patients in perioperative management of these patients (Ishii et al. 2017). A multidisciplinary systems medicine approach may reveal the multilevel complexity of COPD and fill current gaps in optimization of therapy for persons at risk and those with established airflow limitation. Precise clinical "personalised" assessment, with a special focus on understanding the clinical problem, addressing extra-pulmonary morbidity and managing behavioural challenges, such as non-adherence to inhaled steroid treatment, is just as critical to precision medicine in airways disease as targeting the right drug to the right patient.

The relationship between lung microbial environments and COPD exacerbations can be targeted in precision medicine treatments for frequent-exacerbator patients. During consideration for implementation of personalized medicine for patients with OLD, we should consider individual barriers like: physical limitation, psychosocial disease, motivation and attitude *vs.* individual enablers like selfregulation, achievements, autonomus motivation and controlled motivation (Wouters et al. 2018).

For patients with OLD in perioperative period especially before the anesthesia targeting to stable airway situation can result in better anesthesia outcome and decreased postoperative complications.so personalized medicine help to

understanding the underlying pathobiology both for defining disease endotypes and for appropriately targeting therapies to individual patients.

Sleep Apnea and Personalized Medicine

Recently performed studies showed that the "excessively sleepy" subtype was associated with a more than threefold increased risk of prevalent HF compared with each of the other subtypes. Symptom subtype was also associated with incident CVD, coronary heart disease which is important in implementation of therapeutic interventions (Sánchez-de-la-Torre et al. 2015). So, exploring the relationship between excessive sleepiness, physiologic phenotyping and biological markers of oxidative stress and inflammation may also yield important insights. Recently many studies performed in adults and children with OSA using proteomics, studies on miRNA in patients with OSA and resistant hypertension, the application of system biology to genetic studies of OSA and studies on visceral fat transcriptome to assess the molecular basis of the interaction between OSA and obesity (Sánchez-de-la-Torre et al. 2015). Based on this approach we can use anatomical interventions, targeted combination therapy (oxygen, upper airway muscle training, hypoglossal nerve stimulation, drugs to increase upper airway muscle activity, loop gain or increase arousal threshold, mandibular advancement splint) based on patients characteristic (Bonsignore et al. 2017).

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Electronic Health Records

EHRs can store much more information than paper records, and therefore appropriate care is required to keep the information concise to avoid hiding important data among the extraneous patient history. Security should be taken seriously, as electronic forms are more susceptible to security attacks. Creating a partnership between investigators to integrate EHR analysis with clinical research and biomarker identification, multi OMICs analysis, to better understand basic mechanisms of disease could create a powerful approach to identify new treatment options for patients with lung disease (Sulmasy et al. 2017).

Microbiomics and Personalized Anesthesia

Human would basically have two genomes: the human genome and the microbiome; therefore, the changes in the microbial population of the microbiota would result in the manifestation of dysbiosis and, therefore, in the subsequent onset or

flare-up of diseases (Eckerle et al. 2017). Previous studies showed that anesthesia and surgery can induce dysbiosis which is an important risk factor for the pathophysiology of the three most common causes of readmission after gastrointestinal surgery: surgical site infections, ileus, and anastomotic leak (Angulo et al. 2019). Also there are so many studies showed that gut microbiota can contribute to development of ARDS and obstructive lung disease. So considering microbiomics in perioperative medicine not only can improve our anesthesia situation but also could decrease the different postoperative complications.

It is accepted that gut microbiota plays a critical role in the development of pain. Although our understanding of the role of gut microbiota in pain is still in its early stages, emerging evidence suggests that dysregulation of gut microbiota participates in visceral pain, inflammatory pain, neuropathic pain, migraine, and opioid tolerance (Fischbach 2018). So, modulation of gut microbiota by diet and pharmabiotic intervention offers a promising approach to the management of chronic pain in perioperative medicine and toward targeted anesthesia.

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Chapter 6
Personalized Medicine in Pain Management

Stephen Campbell and Daniel Pak

Introduction

Before we can understand the treatment of chronic pain and the role for personalized medicine, we have to define the key mechanisms underpinning pain perception. The body perceives and classifies noxious stimuli through nociception, whereby receptors in the periphery relay information along afferent nociceptive neurons to the spinal cord. Ascending pathways carry this information from the spinal cord to the brain, where cortical pathways provide a mechanism for emotion and cognition to play a role in further processing the painful stimulus. Furthermore, endogenous analgesics may be released as part of descending inhibitory mechanisms, thus allowing the brain to modulate nociceptive transmission.

The perception of pain is a critical function of the body's nervous system. Information about the location, intensity, and quality of a noxious stimulus may warn the body of active or imminent tissue damage. Occasionally, the nervous system may adapt after a prior painful experience in anticipation of future painful experiences. This is accomplished by structural, functional, and chemical changes within the peripheral and central nervous systems. Although these neuroplastic changes may allow for easier detection of noxious stimuli and more efficient transduction of nociceptive signals, they are oftentimes maladaptive and may lead to neuropathic pain syndromes (Campbell and Meyer 2006; Siddall 2013; Talebi and Dabbagh 2017).

Chronic neuropathic pain is a frequent source of chronic pain and reflects both peripheral and central sensitization mechanisms. Peripheral sensitization is a term that describes the abnormal neuroplasticity that occurs in the peripheral nervous

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system, while central sensitization describes that which occurs in the central nervous system. By definition, neuropathic pain is characterized by damage to neural tissue, whereas nociceptive pain involves nonneural tissue (e.g., inflammatory pain from osteoarthritis). As a consequence of the neuroplastic changes seen in neuropathic pain, the perception of pain, in terms of magnitude, location, and quality may become altered. In other words, the experience of pain can be decoupled from the stimulus in the periphery. Pain may be evoked from stimuli that should not reach the nociceptor threshold magnitude, or pain may be elicited in the complete absence of a stimulus. These phenomena are classically seen in patients who experience phantom limb pain after an amputation (Subedi and Grossberg 2011). Because the pain is perceived outside the context of obvious nociceptive input, effective treatment remains a challenge.

The complex neural relay of action potentials from peripheral receptors to the dorsal root ganglion to the central nervous system involves many neurotransmitter and protein targets for pharmacologic therapy. However, pharmacologic treatment options lack anatomic specificity. Moreover, surgical techniques are often limited in that they cannot address pain in patients who lack sensory discrimination, pain localization, and other symptoms related to pathological changes in the nervous system. For this reason, there is a need for treatments with anatomical and pharmacological specificity that are tailored to the individual patient. Namely, personalized medicine, in the context of treating chronic pain, accomplishes this goal via cell-based and gene-based therapies. The goal of this chapter is to explore these novel therapies while also reviewing the pathogenesis of chronic pain.

Peripheral Sensitivity

Pain signal transmission begins with noxious stimuli, which causes the release of inflammatory markers that then act on peripheral nociceptors. Action potentials are carried along high threshold primary afferent neurons, such as Aδ or C fibers, before reaching the spinal cord. Peripheral sensitivity occurs when the threshold for neuronal excitation is lowered, thus permitting minor stimulation to incite pain. After a noxious insult and resulting cell death, hydrogen ions and inflammatory cytokines such as prostaglandin E2, TNF alpha, and interleukin 1 beta are directly released into the extracellular environment. With strong nociceptive input, neuropeptide substance P is released and further modulates pain signaling. Specifically, substance P promotes bradykinin release and facilitates histamine release by causing mast cell accumulation and degranulation. This results in increased vascular permeability and spread of inflammatory mediators to nearby peripheral neurons. It is believed that increased inflammatory molecules in the surrounding milieu alters threshold voltages for membrane channels, in addition to affecting intracellular signaling pathways. In the current theory of peripheral sensitization, this mechanism accounts for the hyperexcitability in peripheral nerves that can occur after tissue damage (Riley and Boulis 2006; Sahbaie et al. 2009; Li et al. 2012; Taghizadeh et al. 2019).

Central Sensitization

Central sensitization is conceptually similar to peripheral sensitization in that the transduction threshold of neurons is lowered, however there are a few key differences. Pain signal transmission in the central nervous system begins with activation of central nociceptors (e.g. AMPA, kainate, metabotropic glutamate receptors, and N-methyl-D-aspartate receptors) in the dorsal horn of the spinal cord in response to glutamate released by peripheral afferents—NMDA receptors are typically inactive during normal ascending pain transmission (Riley and Boulis 2006). However, with prolonged or high-frequency stimulation of these central nociceptors, rostral transmission may continue long after the inciting stimulus is removed. This is thought to occur because of NMDA receptor activation, which is enhanced in the presence of inflammatory mediators. Furthermore, second order neurons in the dorsal horn may become activated by non-stimulated sensory fibers in the periphery. This is termed heterosynaptic potentiation (Woolf 2011). Heterosynaptic potentiation explains why an individual may start to experience pain in an uninjured part of the body (secondary hyperalgesia). Patients may also experience increased pain sensitivity (allodynia) as a result of lower activation thresholds in afferent nociceptive fibers. Allodynia and secondary hyperalgesia are the sensory manifestations of central sensitization and synaptic plasticity (Siddall 2013).

Another important feature of central sensitization is that it impairs descending pain modulation, and this impairment can lead to amplification of the pain experience (Meeus and Nijs 2007). Descending pain modulation refers to the release of endogenous opioids and other neurotransmitters from brain stem structures (i.e., periaqueductal gray matter and the rostral ventral medulla) such as norepinephrine and serotonin. Increasing evidence reinforces that the putative mechanisms of central sensitization and its effect on the disruption of top-down modulation provide a neurobiological basis for the development of chronic pain (Campbell and Meyer 2006; Riley and Boulis 2006; Gangadharan and Kuner 2013).

Endogenous Analgesia

To better understand the new strategies of treating chronic pain that will be presented later in the chapter, it is useful to review how the body promotes endogenous analgesia and antinociceptive effects. Endogenous opioids such as endorphins, dynorphins, and enkephalins act on mu, kappa, and delta receptors, respectively. These receptors are located in both the peripheral and central nervous systems, and they function to inhibit ascending spinal transmission from noxious stimulation of sensory afferents. Soon after, acute tissue damage and transmission of pain signals to the brain, antinociceptive mechanisms are activated. Specifically, the dorsal horns receive noradrenergic and serotonergic input via descending pathways, while also

receiving projections from non-nociceptive afferents and inhibitory interneurons, which use GABAergic and glycinergic signaling. Study of the body's sites and mechanisms of intrinsic pain attenuation has led to conceptual models for chronic pain treatment and a therapeutic basis for exogenous treatment modalities (Riley and Boulis 2006; Gangadharan and Kuner 2013).

Personalized Medicine

Despite the tremendous progress made in pain research in recent decades, current drug therapies for treating chronic pain have very limited efficacy. As a consequence of peripheral and central sensitization and the resulting aberrance in pain circuitry, there is a spatial and temporal abstraction of pain that occurs independent of true tissue injury (Riley and Boulis 2006; Basbaum et al. 2009; Nasseri et al. 2016; Taghizadeh et al. 2019). Pain that is not linked to any obvious active insult on the body is only one of the barriers to effective treatment. Common drug classes for treating nociceptive pain include opioids, non-steroidal inflammatory drugs (NSAIDs), and paracetamol. NSAIDs and paracetamol are thought to treat pain by inhibiting cyclooxygenase and thus inhibit production of prostaglandin, an important molecule in the pathogenesis of peripheral sensitization. Opioids exert a central effect by acting on mu opioid receptors in the dorsal horn of the spinal cord. Options for treating neuropathic pain include anticonvulsants, such as gabapentinoids, and tricyclic antidepressants, which increase the norepinephrine and serotonin available for enhancing descending modulation. Antagonists at the NMDA receptor, such as ketamine and magnesium, block rostral signaling pathways that become activated during the central sensitization process. All of the aforementioned exogenous treatments have been in use for many years, and some of them show modest efficacy in treating certain types of pain (Portenoy 2000; Furlan et al. 2006; Noble et al. 2010; Toblin et al. 2011; Dabbagh and Rajaei 2016). However, there are several difficulties associated with generic use of these treatment modalities. Firstly, many of these drugs have major untoward effects, owing to their lack of anatomical specificity and off-target effects. For example, many NSAID users suffer from gastrointestinal injury and cardiovascular effects, while opioid users are at increased risk of addiction, respiratory depression, paradoxical hyperalgesia, and cognitive effects (Portenoy 2000; Noble et al. 2010). Also, given the multitude of chemicals released during pain transmission and the various receptors involved, it is nearly impossible to achieve pharmacological specificity with conventional treatments. These drawbacks are providing the continuous impetus for research on novel therapeutic approaches for the treatment of chronic pain. Personalized medicine, in the context of chronic pain, refers to treatment that is tailored on the molecular and genetic levels for individual patients. A discussion on cell- and gene-based therapies will follow.

Cell- and Gene-Based Therapies

The chief advantage of personalized medicine in the form of cell- and gene-based therapies is that it allows clinicians to achieve anatomic and pharmacological specificity. Consider that a target organ might have multiple tissue types, each having various types of cells, which each expressing different receptors. One might consider ablative surgery as a feasible option; however, all tissue types in the vicinity of the surgical instrument would be destroyed, with no regard for cell type. Alternatively, a pharmacological therapy might be advantageous because a specific receptor type could be targeted. Yet, these receptors may be expressed on other cells far from the target site and have global functions in normal physiology. Stereotactic cell transplantation is a viable solution to this problem, as it offers anatomic and pharmacologic specificity.

The rationale for the use of cell therapy for the treatment of chronic pain stems from the observation that implantation of adrenal chromaffin medullary cells in the spinal arachnoid space of rats decreased the production of markers implicated in central sensitization and reduced chronic pain behaviors (Eaton 2004; Riley and Boulis 2006; Goins et al. 2012). Adrenal chromaffin medullary cells are ideal because of their intrinsic ability to secrete antinociceptive agents and other important neurotransmitters, such as those discussed under section "Endogenous Analgesia." These cell grafts may be taken from a cadaver or directly from the patient, however incomplete homogeneity of the graft tissue was a limitation in early studies (Eaton 2004). "Purification" of the graft may be accomplished by genetically modifying it after the harvest but before transplanting it to the patient. This process is called *ex vivo gene transfer*. For example, a group of cells would be harvested and then immortalized, a process which describes the induction of a mutation that allows the cell line to have an indefinite replicative capacity—immortalized cell lines are different from stem cells which have a natural ability to divide indefinitely before giving rise to specialized cell types (i.e., without requiring a mutation). Nonetheless, genes that code for production of antinociceptive peptides could then be transferred to these bioengineered cell lines, which are then implanted to the patient's central nervous system by intrathecal injection. Alternatively, genes can be directly inserted into the cells of the patient's parenchymal tissue in a process called *in vivo gene transfer*. A common method for delivering genes involves a viral vector, making use of a virus's natural ability to invade cells and transport genomes. For example, synthetic genes that code for opioid peptides have been placed in Herpes simplex virus (HSV) vectors and injected into the subcutaneous tissue of rodents (Goins et al. 2012). These vectors are taken up by peripheral sensory neurons and travel by retrograde axonal transport to the dorsal root ganglion, where these opioid peptides have been shown to provide an analgesic effect in neuropathic pain models (Wolfe et al. 2007). Similar studies have been carried out with adenovirus and retrovirus vectors (Goins et al. 2012).

Analogous to an intrathecal pump, which is a device surgically placed in a patient's subcutaneous tissue and delivers medication into the cerebrospinal fluid through a catheter positioned around the spinal cord, "cellular minipumps" for

specific analgesics allow for secretion of endogenous opioids and other neurotransmitters that serve to modulate pain transmission (Hino et al. 2009; Chattopadhyay et al. 2011). Compared to implantable prosthetics, these microscopic pumps obviate the need for pump maintenance (e.g. refilling and battery changes) and carry little risk for catheter-related infections.

Summary and Future Directions

Evidence for the role of cell-based therapies involving ex-vivo and in-vivo gene transfer looks promising in animal models, although it remains unclear in small experimental studies involving humans. Recent studies, however, have demonstrated clinical translation of stem cell gene therapy for patients with chronic pain. In particular, bone marrow stem cells (BMSCs) have been shown to have immunoregulatory properties and promote strong analgesic effects when injected intrathecally (Huh et al. 2017). This role for BMSCs is borne of the recognition that proinflammatory molecules activate intracellular cascades involved in central sensitization and the transition from acute pain to chronic pain. In a pilot study looking at ten patients with chronic back pain and radiographic evidence of lumbar disc degeneration, injection of autologous stem cells, harvested from the patient's iliac crest, into the nucleus pulposus area resulted in a statistically significant reduction in pain scores up to 12 months post injection (Orozco et al. 2011). These were all patients who did not respond to conservative treatment. In another study, a phase II clinical trial, 11 patients with spinal cord injuries and documented neuropathic pain received three separate administrations of autologous BMSCs in the subarachnoid space via lumbar puncture. All patients experienced a decrease or a complete resolution of neuropathic pain symptoms at the latest follow up interval at 10 months (Vaquero et al. 2018). Although these are small studies, both demonstrated that BMSCs may be efficacious in treating chronic pain. Given the paucity of human trials looking at cell-based therapies in this context, these exciting early clinical results give us a lens for the future direction of the clinical management of chronic pain.

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Chapter 7
Pediatric Personalized Anesthesia

Bita Malekianzadeh

Introduction

Neonatal and pediatric anesthesia is an important issue. Because this group of population is in growth and developmental stages, they are prone to perioperative complications. Millions of pediatric surgeries are annually performed worldwide. In the USA, 6 million children undergo surgery each year, among them, 1.5 million are infants. Different drugs are used in daily practice by pediatric anesthesiologists. The safety margin of these drugs is very narrow and anesthetic agents can produce various responses in different children. Combining anesthesia agents to achieve ideal anesthesia with minimal complication is still considered a challenge in pediatric patients. Traditional approaches do not always lead to an ideal clinical response. Another important aspect in pediatric anesthesia is the issue of potential effects of anesthetic drugs on developing brain; the FDA has announced some warnings about neuroapoptosis in children younger than 3 years old and fetus of pregnant women during their third trimester who undergo repeated or prolong general anesthesia or sedation.

Personalized medicine has created a revolution in the practice of anesthesia and perioperative care especially regarding its paramount role in pediatric patients. Recent advantages in omics science have opened a new horizon in pediatric medicine (Ama et al. 2010; Galinkin et al. 2010; Chidambaran et al. 2012; Andropoulos and Greene 2017).

In this chapter, the basic and current understanding of pharmacogenomics, epigenomics, proteomics, metabolomics, and interactomics relevant in perioperative practice for infants and children are discussed.

Some aspects of this question will be addressed: why the similar patients have very different perioperative responses and complications?

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Nowadays, it is believed that each child is unique, and he/she should benefit from the best perioperative care.

Preoperative Care

The Goal of Providing Preoperative Anesthetic Care

Newborn infants, babies, and children are special population groups that should be given special attention during the pre-operative visits. Proper evaluation and preparation in this group of patients before surgery are of significant importance. One of the purposes of visiting patients before the surgery is to identify factors, which may increase the risk of anesthesia and by administering the interventions, this risk can be lowered. The second purpose is to establish a relationship between the anesthesia specialist and the patient and his parents, which can help to relieve the patient's stress before the surgery, which can, in turn, improve the outcome. The condition of the patient and his/her family should be optimized (Serafini et al. 2014; Basel and Bajic 2018).

Monitoring

Traditional Approach

Throughout the pre-operative care, a number of laboratory tests are requested according to the patients' conditions and clinical examinations, and anesthesia plan should be prepared for each patient. Pre-operative evaluation starts with examining patients' history. For this purpose, patient and his family were interviewed and any current disease and his past medical history were recorded. Issues such as cholinesterase deficiency, malignant hyperthermia, and other side effects of anesthesia in the patient and his family are scrutinized. Also, the patient and his family's smoking history, record, medicine use, and detailed account of their allergies are important. In the review of system and physical examination, pre-maturity, BPD, airway problems, cardiovascular, pulmonary, musculoskeletal, gastrointestinal, kidney, hematology, oncology, metabolic, and endocrine were evaluated and the patient's circumstances according to his underlying disease, and optimized and the necessary paraclinical tests are requested.

It seems that conducting laboratory tests on a regular basis before the operation cannot significantly affect patients' outcome; and the tests selected based on the patients' history, circumstances, and operation type can have a more positive effect.

Routine hemoglobin for most elective operations have no indications and it is usually measured in patients who are quite expected to bleeding during the

operation, patients with hemoglobinopathy, pre-term neonates, and infants under 5–6 months. Coagulation tests including counting the number of platelets, INR (international normalized ratio), PTT (partial thrombin time) are not recommended for patients who have no coagulopathy, as it cannot be an accurate criterion in identifying the patients at the risk of bleeding. These tests can be employed before major reconstruction operations, patients with bleeding history, or for tonsillectomy at some centers (Bamedi et al. 2017; Bogusaite et al. 2018; Nelson et al. 2018; Zhong et al. 2018).

Current risk stratification, which can be determined based on the history and patient examination comorbidities, and the operation circumstances account for only a small part of the issues involved perioperative (Bilkey et al. 2019).

Personalized Medicine Approach

Adverse drug reaction (ADR) in children due to their pharmacokinetic and pharmacodynamic complexity during development, is an important issue. Genetic differences among people can determine the susceptibility to perioperative events. Genetic is equal to 20–95% of individual differences in response to the medicines. Personalized pre-operative evaluation should be started before the operation. Regarding, this is quite novel about children and new-born babies. As the human genome project completed, it is hypothesized that the treatment can be administered according to precise molecular changes. Although genomic discoveries have affected different areas of medicine such as cardiovascular, neurologic system, metabolic diseases, and cancer, it has not been paid attention in the anesthesia field (Nashibi et al. 2016; Mottaghi et al. 2017; Safari et al. 2017). It seems that it is the ripe time for all the pediatric patients to have gene sequence as a standard preoperative workup just similar to the other experiments as follows: hemoglobin, electrolytes, etc. Every person undergoes this experiment once in his lifetime, and its results can be used forever. In the future, the specific functions of pharmacologic can be determined using one blood sample; and accordingly, the right decisions can be made on drug prescription and proper dosage. The process of taking care of patients and the clinical outcome will improve the use of this approach (Gabriel et al. 2017; Iravani et al. 2017; Bilkey et al. 2019; Sezari and Dabbagh 2019).

Point of care test (POCT) includes the tests performed near the patient and frequently at the bedside. So far, perioperative POCT has included the following: arterial blood gas monitoring, chemistry, the co-oximetry panel, parathyroid hormone assay, and coagulation testing such as thromboelastometry (ROTEM), thromboelastography (TEG) (Rhee and Kahn 2010; Shaw 2016; Arboleda and Garner 2017).

This technology is developing in recent years, and it has been used by some companies to analyze genetic polymorphism that can affect drug metabolism. The practical example is CYP2D19 analysis, which activates clopidogrel. CYP2D19 different alleles impair the enzyme's ability to metabolize the drug and lead to side effects (Roberts et al. 2012; Naderi et al. 2016).

POCT (Point of Care Testing) is so helpful for the anesthesiologist to make a perioperative quick decision due to the rapid preparation of results. However, there may be some concerns about its accuracy. POCT is performed by the clinical staff, not by trained laboratory personal, but if it is done with controlled quality, it can be very practical (Shaw 2016).

PG screening can be directly transferred to EHR (electronic health record). By studying and examining the Electronic Health Record, anesthesia specialist can prescribe the drugs with respect to the patients' pharmacologic and can also employ preoperative pharmacogenomic in the daily practice (Gabriel et al. 2017; Iravani et al. 2017; Bilkey et al. 2019; Rahmatizadeh et al. 2020).

The reasons for patients readmission to the GOLDILOKs (genomic and ontogeny-linked dose individualization and clinical optimization for kids) clinic from 2010 to 2016 has been studied, respectively. In addition to other causes, ADRs (adverse drug reactions) and inappropriate response to medication was important referral cases. Most patients were Caucasian men. In these patients, pharmacogenetics was widely used as a treatment guide. The patients were evaluated by multidisciplinary pediatric personalized medicine. However, pharmacogenetic tests are not the only means of precision treatment in children; and the identification of many pharmacodynamics errors such as drugs interfere with the receptor, is not available (Sandritter et al. 2019).

Single nucleotide polymorphism (SNP) is a substitution of a single nucleotide that occurs at a specific position in the genome. SNPs are the most genetic variations among individuals and can cause susceptibility of individual differences to certain diseases such as thalassemia, sickle cell anemia, and cystic fibrosis. A polymorphism can affect the drug action at any organ of the body. Polymorphism can be in the form of SNP, as a substitution of a single nucleotide base pair on an entire chromosome to multiple inherited linked base pair changes (a haplotype). A single nucleotide polymorphism can alter the absorption, metabolism, drug transport, or receptor site; and has a profound effect on the drug action. The function of some perianesthetic drugs is altered by gene polymorphism (Table 7.1) (Shenfield 2004; Galinkin et al. 2010; Dabbagh and Rajaei 2013).

Premedication

The Traditional Drugs

Benzodiazepines: midazolam is a benzodiazepine with rapid onset; however, it has short effects. It is frequently used in pediatric anesthesia as oral premedication. Through binding GABA in CNS, midazolam has sedative, anti-stress, amnesia, and hypnotic effects. Children show quite different reactions to midazolam. It is quite likely that it serves as a stress-reliever; however, it has not proven to be effective in another patient or even side effects such as paradoxical reactions may be observed (Shin et al. 2013b; Pacifici 2014).

Table 7.1 Clinically relevant gene polymorphism of perioperative anesthetic drugs

Drug	Gene	Effect of polymorphism
Midazolam	CYP3A4 CYP3A5	Clearance reduction
Dexmedetomidine	CYP2A6 ADR2C	Lower efficacy
Propofol	UGT1A9 5HT2A	Higher induction dose Shorter onset time
Ketamine	CYP2B6	Decreased metabolism
Inhalation agents	CYP2E1	No significant clinical effect
N2O	MTHFR	Homocysteine elevation
Fentanyl	CYP3A4	Variation in drug response
Local anesthetics	SCN5A	LA resistance
Succinylcholine Mivacurium	Bche	Clearance reduction
Rocuronium	SLCO1B1 ABCB1	Prolonged recovery time
NSAIDS	CYP2C9 CYP2C8	Metabolism reduction
Ondansetron Granisetron	CYP2D6 multicopy	Rapid metabolism

Midazolam is metabolized into its active metabolite, and 1-hydroxymidazolam in the liver by CYP3A4 and CYP3A5 enzymes. These enzymes are not very active in the first weeks of life and the metabolism rate of midazolam is lower in infants compared to older children and adults. The meta-analysis of seven clinical trials showed that environmental factors exert a stronger influence on midazolam deposition compared to CYP3A4/5 (Miao et al. 2009).

However, other studies have shown that CYP3A can affect the pharmacokinetics of midazolam. The effect of genetic polymorphism of CYP3A on midazolam pharmacokinetics was studied in Asian patients suffering from cancer. The results showed that clearance of midazolam for CYP3A*5 with (1*/1* or 1*/3*) expressories were 22% lower than CYP3A5 *3 expression and homozygotes (CYP3A5 1*/1* is the normal genetic status of the enzyme) (Seng et al. 2014). Shin et al. reported that the clearance of intravenous midazolam is reliably dependent on CYP3A5 *3 (Miao et al. 2009).

The impact of CYP3A5 *3 on clearance of midazolam in basal, induced and inhibited conditions were examined. CYP3A5 genotype had no significant effect on midazolam pharmacology under the basal and induced conditions. However, under inhibited conditions created by using Itraconazole in this study, participants carrying CYP3A5 *1 were less likely to undergo clearance changes. People carrying CYP3A5 3*/3* experienced a more significant drop in systematic clearance compared with 1*/1* (Yu et al. 2004).

CYP3A4 is the main CYP in the liver and intestine of human beings and can play a key role in the metabolism of many drugs. This enzyme has many variations in the

public. A new allele, CYP3A4* 22rs with a frequency of 5–7 % in the Caucasian population is accompanied by a drop in CYP3A4 expression and the enzyme activity, and affects statin, tacrolimus, and cyclosporine metabolism. CYP3A4* 22 results in a drop in midazolam metabolism in patients suffering from cancer.

In people carrying CYP3A4* 22, 20.7% lower than CYP3A4 1*/1* and for CYP3A5 *3 and CYP3A4 *22, there is a 38.7% drop in the rate of metabolism of midazolam. In children with CYP3A5 *3 and CYP3A4* 22, a drop in the metabolism of midazolam and its longer-lasting effect was observed (Elens et al. 2013).

Oral lorazepam and temazepam are useful sedatives in older children. Diazepam does not have a clinical application for this purpose, because of its prolonged duration of action (Ronaghi et al. 2016; Chennou et al. 2019; Dave 2019).

Ketamine: ketamine is an NMDA receptor antagonist, used for pediatric premedication. It is an effective sedative and analgesic but isn't amnestic. Ketamine can also cause nausea and vomiting, psychological disturbance and prolonged recovery. Its intramuscular injection used as premedication in uncooperative and combative children (Yuen and Bailey 2018).

There are individual differences, especially regarding the effects of ketamine analgesia. Ketamine is metabolized to its active metabolite, norketamine, through CYP2B6 and CYP2A4 in the liver. CYP2B6 is the major isoform that metabolizes ketamine. The CYP2B6 coding gene is highly polymorphic. The CYP2B6*6 is the most common CYP2B6 gene allelic variant that decreases ketamine clearance and explains the many differences in steady-state ketamine concentration. In chronic pain patients who treated with ketamine, this allele has been associated with a marked decrease of ketamine clearance and an increase in its complications (Li et al. 2015; Cook-Sather et al. 2016; Dinis-Oliveira 2017).

Opioids: the use of opioids is uncommon as premedication in healthy children. Dysphoria, nausea and vomiting, pruritis and respiratory complications should be considered. Oral transmucosal fentanyl citrate has a rapid onset and it is effective as midazolam, however, preoperative opioids use is limited to children with pain. The OMICS approach for opioids will be discussed later, in the analgesia section (Chatrath et al. 2018).

The newer clinical agents: Alpha-2-Adrenoreceptor agonists: dexmedetomidine is employed for creating light sedation and analgesia. It is a highly selective α2 agonist that has been paid lots of attention by children pediatric anesthesiologists as it maintains breathing and causes no apnea. Clonidine is an older alpha2 agonist with a longer duration of action. Hypotension and bradycardia may occur, however, its incidence in the preoperative setting is low (Dabbagh 2011; Moghadam et al. 2012; Jabbary Moghaddam et al. 2013; Su et al. 2016; Afshari 2019).

There are significant differences in sedation caused by dexmedetomidine among people, which is associated with genetic differences. The metabolism of dexmedetomidine is mainly dealt with CYP2A6, α2 adrenoreceptor (ADRA2C, ADR2B, and ADR2A), and UGT (UGT1A4, and UGT2B10). The variance of ADRA2C1291 is related to a longer onset time effect and lower efficacy of dexmedetomidine (Le et al. 2011; Dahmani et al. 2014; Holliday et al. 2014; Andropoulos 2018; Zhou et al. 2018a).

Preoperative Risk Stratification

Over the past decades, different models have been developed to improve pediatric perioperative mortality and morbidity prediction, especially in noncardiac surgeries. Risk stratification scores are estimated by considering the patient's comorbidity and intrinsic risk factors of surgery. The patient's age, prematurity, presence of at least one of the comorbidities (respiratory disease, congenital heart disease, renal insufficiency, neurologic disease, hematologic disease) and urgent surgery are the main items for this purpose; however, the risk assessment tools have a limited mortality and morbidity prediction (Valencia et al. 2019; Nasr et al. 2016).

Omics can be potentially used for individual ***perioperative risk stratification*** in many patients. MicroRNAs are small, non-coding RNAs that regulate gene expression in a specific way. Their function as post transcription regulators is to interfere with target mRNA. Binding of microRNA to protein coding transcripts can prevent the translation of mRNA into a functional protein. In fact, miRNAs mainly act as negative regulators. MiRNAs are involved in all physiological processes including differentiate, proliferation, metabolism, homeostasis, apoptosis, and inflammation. Many of these processes are important in anesthesia and critical care (Zeng et al. 2014; Neudecker et al. 2016).

The role of miRNA transcription in personalized medicine has been considered increasingly much more crucial. Patterns of miRNA emergence suggest new diagnoses, as well as new therapies to target miRNA. Different drug approaches addressing miRNAs are being evaluated in the treatment of various diseases. In pre-operative field, miRNA can be used as preoperative biomarkers to stratify the risks and complications during and following surgery and specific organ damage. Using this risk indicator can help optimizing the anesthesia and operation conditions, and prevent acute organ damage and severe inflammatory responses. MiRNAs can be employed in the daily practice of anesthesia and critical care for different patients (Twaroski et al. 2014). The role of miRNA in neuroprotection has been studied in various studies and it can be of significant importance in the field of infants and children anesthesia (Huang et al. 2014).

Shortly after the discovery of miRNA in 1993, its profile studies revealed the association between miRNA expression and various diseases in humans. Various studies have shown that miRNA plays a critical role in human cardiovascular disorders including myocardial infarction, fibrosis, and heart failure. The role of miR-155 in the development of atherosclerosis is well known. MiRNA-208a is an important regulator and modulator of cardiac stress response, and plays a specific role in regulating myocardial function. Accordingly, its genetic deletion showed a decrease in hypertrophy and fibrosis in response to cardiac stress in mice (van Rooij et al. 2007; Aghajani et al. 2017). MiRNA-208a up regulation leads to increase in incidence of βMHC (myosin heavy chain), and increases the risk of arrhythmia and fibrosis; therefore, it is a strong predictor of cardiac death and heart failure (Callis et al. 2009; Satoh et al. 2010).

LNA (Locked nucleic acid) is a pharmacological inhibitor of miRNA 208a that has been tested in vivo and specifically targets this miRNA (Montgomery et al. 2011). Reduced expression of miR-208a increases the resistance to high-fat obesity and can be used in the treatment of metabolic syndrome. The MiRNA-208a inhibitor can increase the level of mediator complex subunit 13 (Med13), which is involved in regulating energy expenditure and various cardiac balance genes (Grueter et al. 2012).

In children with arrhythmia, paroxysmal or persistent tachycardia are common, and can result in heart remodeling and heart failure. MiRNA1 can be a good predictor of supraventricular tachycardia in children. Patients with SVT have lower level of miRNA1. MiRNA-133 can more accurately predict ventricular single-cardiomyocytes, and this biomarker shows higher levels in VT. In animal models, miRNA1 is elevated in acute MI and is associated with ischemia-induced arrhythmias. Arterial pulmonary hypertension leads to right heart failure. More than 30 circulatory miRNAs are associated with the development of pulmonary hypertension, and the levels of some of them are consistent with the pulmonary vascular resistance index (Zhou et al. 2018a).

Congenital heart diseases encompasses a wide range of heart disease in infants and children. Different types of congenital heart diseases such as VSD, ASD, TOF, and PDA account for more than 40% of perinatal deaths, and recent evidence has shown the significance of miRNA in CHD. Specific miRNAs are required for fetal heart development and their dysregulation can lead to cardiovascular structural abnormalities. For example, the role of miRNA1-1 and miRNA181 in VSD and specific expression changes of more than 61 miRNAs in the TOF, have been demonstrated (Smith et al. 2015; Sucharov et al. 2015). Increased blood levels of miRNA1 have been shown in congenital heart disease, as predictive of short-term outcome after surgery. MiRNA1 is a new biomarker that can be measured during perioperative period and improves the care taking of CHD (Stoica et al. 2019).

Since ***pulmonary complications*** are the most common postoperative complication in non-cardiac thoracic surgery patients; the risk of these complications has been determined in different ways. MiRNA21, a biomarker of vital role and biological function, has been seen as an early predictor of pulmonary complications such as ARDS in these patients. High levels of miRNA1 are associated with extra-pulmonary complications and death within 1 year (Liu et al. 2016).

Recent studies have shown the important role of miRNA in mediating and modulating the effects of various drugs. CYP3A4 is involved in the metabolism of more than 50% of common prescription drugs, and individuals' response to the drugs is significantly dependent on the level of CYP3A4. Studies on liver biopsy specimens have shown the correlations among four miRNAs and the reciprocal translational efficacy of CYP3A4. MiR577, miR1, micRNA532-3p, and micRNA627 are considered as miRNAs that lead to individual differences in response to CYP3A4 metabolized drugs in the general population (Wei et al. 2014).

The role of proteomics in personalized pediatric anesthesia: the product of the translation of the genes are proteins. There are several millions of unique proteins and the expression of all proteins in a cell, tissue or organism is essential for cell-specific function.

In terms of the physiology and pathophysiology of different cells and tissues, there are different proteomes. In fact, in some cases, the product of initial translation undergoes some types of modification and post-translation modification, which involves a wide range of irreversible reactions. This can be affected by age, environmental conditions, and diseases. Different types of proteins are found in biological or clinical specimens. Protein biomarkers can be measured by new methods including two-dimensional gel electrophoresis or protein microarray chips (Piazza et al. 2013; Atkins and Johansson 2006). These biomarkers should be detected in body fluids such as plasma, CSF, blood, urine, serum, and saliva.

Proteomic analysis allows the proteins of each individual to act as biomarkers playing a critical role in the study of diseases diagnosis processes and also from a prognostic point of view. It contributes to understanding the mechanism of the action of many drugs in anesthesiology and is of significant importance in clinical practice, risk stratification, and response to treatment. It is also widely used in ICU and chronic pain for diagnostic and prognostic cases. New diagnostic tests can be even suggested using proteomic analysis, which constitutes an important component of personalized therapeutics (Giudice and Petsalaki 2019).

Studies in this area on children are not widely available in adults. However, in recent years, several studies of protein risk stratification in children, especially in acute kidney injury after cardiac surgery, have shown that serum creatinine is a delayed marker for acute kidney injury. Preoperative timing is essential in these patients. Preoperative measurement of urinary biomarkers complement factor 8 (CFB) and histidine rich glycoprotein (HRG), significantly improved the risk stratification in these patients (Merchant et al. 2018). Pre-operative IL8 level and post-operative TNFα can be used as a predictor of AKI following cardiac surgery in children over 2 years old. The best method for risk stratification is evaluating the patient and using laboratory data, respectively (Park et al. 2016; de Fontnouvelle et al. 2017).

The Apolipoprotein E (APOE) genotype is associated with brain post-ischemic and brain trauma recovery. APOE gene sits on chromosome 19 and the APOE protein play an important role in neuronal repair. The APOE protein contains lipoproteins and the major lipid transporters in the CNS, and it is known as a key factor in the mobilization, redistribution of cholesterol, and phospholipid remodeling of neuronal membranes. There are three isoforms of APOE (E2, E3, and E4), which are encoded by three alleles (ε_2, ε_3, ε_4). APOEε_2 allele is associated with worsening early neurological outcome after infant cardiac surgery (Gaynor et al. 2014).

Intra-operative Pediatric Care

Anesthesia Induction, Traditional and Personalized Approach

Clinical response to anesthetic agents during induction and maintenance of anesthesia in similar children at the same dose is not identical. In traditional method, the type and dosage of anesthetic drugs are adjusted according to the patient's condition e.g. the patient's weight and comorbidities. Omics is considered in personalized medicine for anesthetized patients, especially in the case of narcotics, which is a great variation in the response of individuals (Kaymak et al. 2008).

Inhalation Induction

Sevoflurane is the most commonly used inhaled anesthetic for induction of pediatric patients; both in infants and children. Sevoflurane is a safe anesthetic agent with relatively low side effects. It has become a popular induction drug, due to ease of administration, rapid onset, less airway irritation and hemodynamic stability. However, the prevalence of emergence agitation with sevoflurane induction is higher than the other anesthetic agents.

Sevoflurane is metabolized by microsomal CYP2E1 in the liver and kidneys. Halogenated inhalation agents reduce hepatic blood flow and sevoflurane anesthesia can cause a mild disorder in hepatocellular integrity.

Glutathione s-transferase (GST) is a liver marker that is elevated in sevoflurane administration, as a cytosolic liver enzyme, and it might enable earlier detection of liver injury. GSTP1 genetic polymorphism has a significant effect on GST serum levels and GSTA1 is associated with an increase of concentration of GST, 24 hours after the end of anesthesia. However, no subsequent studies were performed to select the dose of sevoflurane (Mikstacki et al. 2016; Kaymak et al. 2008; Caplan and Felberg 2017).

Intravenous Induction

Propofol is an intravenous anesthetic with benefits of rapid onset and offset, lower incidence of nausea and vomiting and emergence agitation. It activates the GABA inhibitory neurotransmitters. The usual induction dose is 1–3 mg/kg, depends on the patients age (Chidambaran et al. 2015; van Hoff et al. 2015; Kim et al. 2019). Propofol causes systolic, mean and diastolic blood pressure reduction. There is a substantial individual susceptibility to propofol. Its etiology can be related to genetic polymorphism. A mutation in the 5HT2A gene (rs6313) is along with individual susceptibility to propofol. In carries of the minor allele (G) of 5HT2A rs6313, propofol requirement is lower and the onset time is shorter. Dominant mutations in GABA A1 rs2279020, GABAA2 rs11503014, and CHRM2 rs1824024 are along

with propofol cardiovascular effects (Zhong et al. 2017). On the other hand, it has been showed that UGT1A9-1887-TG variant heterozygotes need larger dose of propofol (Khan et al. 2014). The effect of intraoperative different anesthetics on miRNA expression and proteins is different. Except for the effects of these drugs on neuroapoptosis mediators, the hemodynamic profile may also be related to miRNA expression in cardiovascular system. Propofol and etomidate are intravenous anesthetic agents with different cardiovascular effects. These differences are particularly important for cardiovascular and critically ill patients. MiRNAs up and down regulation were studied in patients who received propofol or etomidate. This study showed that these drugs have different effects on circulatory miRNA. Regarding this, further animal studies are needed to determine which one of the miRNAs changes (Yao et al. 2018).

Due to rapid onset and rapid recovery of propofol, it is a common anesthetic drug for induction and maintenance. However, propofol infusion is not recommended for critically ill children. In recent years, the anti-inflammatory effect of propofol has been considered. Propofol can upregulate Annexin A1 protein, which is an anti-inflammatory protein, and prevent the phosphorylation of P53 and inflammatory factors (IL6, IL1β, and TNFα) release (Tang et al. 2011).

Ketamine is a widely used anesthetic agent that antagonizes the N-Methyl-D-aspartate glutamate (NMDA) receptors. It has many clinical applications, especially providing analgesia and cooperation for short procedures in children, because of hemodynamic stability and preservation of patient's spontaneous breathing. CYP3A4, CYP2B6 and CYP2C9 enzyme isoforms metabolize ketamine through N-demethylation in the liver. Its metabolite is norketamine. CYP2B6*6 allele is associated with a reduction of enzyme expression. It may lead to individual differences in metabolism and clinical response to ketamine (Hijazi and Boulieu 2002; Li et al. 2013). Studies have shown no significant association between genotype and incidence of emergence phenomena. High dose and long duration administration of ketamine, were predictors in this case (Aroke et al. 2017). However, in chronic pain patients who use long duration subcutaneous ketamine, CYP2B6*6 allele was associated with significant reduction in ketamine steady state plasma clearance. It may cause elevation of plasma level and increase in adverse effects of ketamine e.g. increased salivary secretions and cerebrospinal fluid pressure. However, the effect of this allele on precision medicine and ketamine is still controversial (Li et al. 2015; Cook-Sather et al. 2016). Ketamine induced neuronal apoptosis will discussed in the neuroapoptosis section.

Muscle Relaxants

Since introducing succinylcholine to clinical practice in 1950, it has been used as a gold standard drug for rapid and profound muscle relaxation. Succinylcholine is considered for rapid sequence induction, due to its rapid onset and short duration of action. Succinylcholine adverse effects such as prolonged muscle paralysis and fatal

hyperkalemia were reported from the same decade. It recommended for emergency control of the airway in infants and children (Dierdorf and McNiece 2018).

Succinylcholine and mivacurium (a short acting non depolarizing neuromuscular blocker) are hydrolyzed by plasma cholinesterase. Also, butyrylcholinesterase heterozygote variant expression leads to less effect of this enzyme and prolonged recovery time after succinylcholine and mivacurium administration. In homozygotes, this time can be up to 60 times longer(Palmer et al. 2005). Pseudocholinesterase deficiency will discussed later.

Individual differences, resistance and sensitivity in the response to muscle relaxants aren't uncommon. Except of the nature and properties of muscle relaxants, individual factors including age, sex, smoking, race, nutrition, obesity and body temperature can affect onset time of neuromuscular blockers (Kim et al. 2017).

In the case of nondepolarizan muscle relaxants, a study was performed by considering the association of liver transporter polymorphism and its effect on the clinical use of rocuronium. SLCO1B1, ABCB1, and CHRNA1 polymorphism has no effect on rocuronium onset. In patients with ABCB1 rs1128503TT, SLCO1B1 rs2306283 AG, and GG genotype; recovery time is prolonged. Accordingly, the most important genotype with effect on rocuronium is ABCB1 rs1128503C>T (Mei et al. 2015; Awad et al. 2019).

Pseudocholinesterase Deficiency

Butyrylcholinesterase or pseudocholinesterase is an enzyme produced in the liver and can be found in most of the tissues except red blood cells. The defect of this enzyme can be hereditary or acquired. The most obvious clinical effect of pseudocholinesterase deficiency is prolonging the effect of relaxants including mivacurium and succinylcholine. Among pseudocholinesterase deficient patients, the defect cannot be diagnosed until they are exposed to succinylcholine or mivacurium. In these patients, prolonged paralysis and apnea are observed after the administration of these drugs (Zhang et al. 2018).

Pseudocholinesterase deficiency is important to the anesthesia providers including emergency department, anesthesiologists, and intensive care unit. In acquired cases, this defect was due to chronic infectious, kidney disease, hepatic disease, malnutrition, cancer, severe burns, or using a variety of drugs. In neonates, blood levels of the enzyme are usually lower.

Inheriting the defect of pseudocholinesterase is autosomal recessive that is associated with mutations in the butyrylcholinesterase gene BChE, which lies in q 26.1–26.23 position in ch3. Accordingly, Polymorphism of this gene has many variations. An individual can inherit 65 variants and their clinical pattern ranges from mild to severe paralysis and apnea. 96% of the population are homozygote for normal pseudocholinesterase, which is EuEu designate. The remaining 4% carry atypical alleles as heterozygote or homozygote (Zencirci 2009).

The most common variant is the Atypical variant A in which mutation occurs at nucleotide 209 and Guanine replaces Adenine and Glycine substitutes for Aspartic

acid at position of 70 of the enzyme. The Kalow variant (variant K) can reduce the enzyme level by 30%; and other types are fluoride and silent resistant. In the traditional method, the patient and his family history of prolonged anesthesia and apnea is examined.

Blood sample and the activity of pseudocholinesterase enzyme, which is measured using a dibucaine and fluoride inhibition test, are employed for diagnosis. Although DNA analysis is not routine, it can be used to diagnose a variety of genetic defects such as heterozygotes or atypical alleles. New variants of the butyrylcholinesterase genotype are being discovered (Alvarellos et al. 2015).

A study on a 12-year-old child and his family has shown a new mutation. Two heterozygous mutations had occurred and stopped the translation and production of active protein (double heterozygotes recessive mutation).

- Exon2, C.734> T and C.401-402insA

This mutation can be related to the intellectual disability phenotype (Yu et al. 2018).

Malignant Hyperthermia

Malignant hyperthermia is a pharmacogenetic disorder in metabolism of calcium in the skeletal muscle, and it is a particular concern to a pediatric anesthesiologist.

Accordingly, it was first introduced as a clinical entity by Denborough in 1960. An Australian young man who was afraid of anesthesia due to the death of several members of his family, had symptoms such as hypotension, tachycardia, and high fever during anesthesia. However, he was rescued using aggressive cooling, and genetic tests showed that a dominant autosomal disorder is the main reason underpinning death during anesthesia. This disorder starts with MH triggers (volatile anesthetics or succinylcholine) and is rarely associated with hypermetabolism symptoms and death in the absence of medications and anesthetic triggers.

The symptoms of malignant hyperthermia emerge as hypermetabolic creases with rapid onset and uncontrollable release of myoplasmic calcium of skeletal muscle cells. If predisposition for MH is diagnosed in the patient before anesthesia, it is preventable (Rosenberg et al. 2015; Kaur et al. 2019). Molecular etiology and genetics of MH have made significant progress in the recent decades.

RYR1 (ryanodine receptor1), CACNA1s (calcium voltage gated channel subunit alpha1s), and STAC3 (stromal antigen3) are three genes associated with susceptibility to MH. The RYR1 gene encodes the Ryanodine receptor of skeletal muscle. Ryanodine receptors mediate the release of calcium ions from sarcoplasmic reticulum and endoplasmic reticulum, which is an essential step in muscle contracture. Mutation of this gene is located at chromosome 19q13.2 and is associated with various diseases, pharmacogenetic disorder, malignant hypertension, and three congenital myopathy, including Central Core disease (CCD), and Multiminicore disease (MMD), an isolated case of congenital myopathy (Robinson et al. 2006; Toppin et al. 2010; Riazi et al. 2018).

A coagulopathy disorder with a variant of RYR1, which is implicated in predisposition for MH, has been recently reported. This report has increased the spectrum of clinical disorder, which currently includes myopathies and exertional rhabdomyolysis. The RYR1 Ryanodine receptor is mainly found in skeletal muscle, but it can also be seen in smaller quantities in immune cells and smooth muscles, and it is hypothesized that RYR1 mutations have wider effects compared to those that have been previously identified (Lopez et al. 2016).

A small number of MH-prone families carry a variant in the CACNA1s gene, which encodes the α-1 subunit of voltage-dependent channels (α-1subunit of the T tabular cell voltage-gated Ca+ channel). It is also known as the dihydropyridine receptor. α-1 subunit is very important for voltage sensing and conduction of hydropyridine receptor (Stewart et al. 2001; Gillies et al. 2015).

Approximately 50% of MH probands rescued from an MH and individuals who are MH-prone based on the contracture tests that carried no RYR1 or CANCA1S variants and their genetic basis remain unknown to MH (Klingler et al. 2014; Rosenberg et al. 2015).

Stac3 protein is required for excitation-contraction coupling in skeletal muscle. Its function is due to effect on CACNA1channel activity and also normal calcium release from the sarcoplasmic reticulum (Fig. 7.1). A homozygote STAC3 mutation

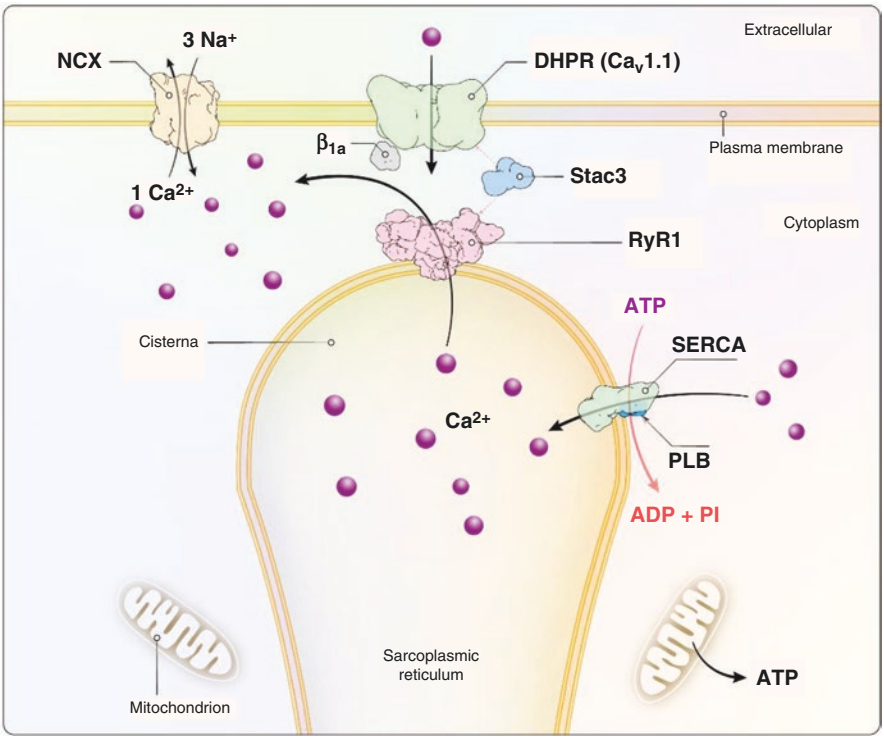

Fig. 7.1 DHPR, Ryanodine receptor and stac3 protein interaction in excitation-contraction coupling

has been recently linked to the American native myopathy, which was associated with predisposition for MH in a Native American family (Horstick et al. 2013).

STAC3 encodes stac3 protein and it is necessary for the efficient arrangement of dihydropyridine receptors and RYR1s. Also, the necessary components of skeletal muscle excitation contraction coupling underlying MH are the interruption of excitation contraction coupling and the sudden and severe increase in toxic sarcoplasmic calcium via RYR1, which occur in response to the endogenous or exogenous stimulus. Currently, more than 200 RYR1 variants have been found in association with MH, but only 35 RYR1 variants and 2 CACNA1s variants were recognized as being functionally characterized to be used in diagnostic genetic testing for MH (Gillies et al. 2015; Hopkins et al. 2015; Riazi et al. 2018).

Anyone carrying one of the MH pathogenic variants is susceptible to MH. When a variant of the familial pathogen is identified, genetic testing is required for all the family members. However, having a predisposition for MH cannot be rejected for those who are not carriers of the familial variant, because there is a possibility for more than one pathogen variants in the same family. Therefore, a contracture test must be done for these patients. Accordingly, DNA-based MH susceptibility detection is an attractive choice, especially in children as it can be an alternative to muscle biopsy and in vitro contracture caffeine halothane test (Stowell 2014).

Maintenance of Anesthesia, Traditional and Personalized Approach

Amnesia

Midazolam is a water soluble, short acting benzodiazepine that provides amnesia during children's anesthesia. It is metabolized in the liver through CYP450 enzyme. Clearance of midazolam, significantly depends on the patient's age. Preterm infants have the lowest metabolism rate, due to immaturity of CYP3A4 metabolism. Midazolam pharmacogenomic has been discussed in preoperative section (Shin et al. 2013b; Brussee et al. 2018).

Analgesia

The response of pediatric patients to opioids is highly variable. In addition to immaturity of organs such as brain and liver in neonates and its important effect on drug metabolism; pharmacogenetic issues are also important. A well-known pharmacogenetic example of pediatric morbidity is the administration of codeine conventional doses to ultra-rapid metabolizer children. In ultra-rapid metabolizers, most of the prodrug become active form and toxicity sharply increases. This will be discussed in pediatric personalized pain management (Kirchheiner et al. 2007; Iravani et al. 2017).

Fentanyl is a common and potent narcotic for pediatric intraoperative analgesia due to more hemodynamic stability compared to morphine and the other opioids. it is metabolized by CYP3A4/5. The patient's response to fentanyl and perioperative dose is highly variable (Mieda et al. 2016). Fentanyl clearance has decreased in preterm infants, but reaches to 80% of adults in term infants.

Synthetic opioids dose should be reduced in the first 4 weeks of life and for premature infants at least until to 44 weeks post conceptual age. Remifentanil is metabolized by nonspecific plasma and tissue esterase and has a very short half-life. The importance of liver and kidney maturity is negligible. Its metabolism is not affected by butyrylcholinesterase deficiency. Effective half-life of remifentanil in neonates is similar to older children and adults and it requires no dose adjustment (Kamata and Tobias 2016; Cravero et al. 2019).

Morphine

Morphine is a practical opioid to control pain in pediatric patients. There is a large variation in its pharmacokinetic in neonates and young infants. Morphine dose should be adjusted in neonates, because of lower glomerular filtration rate and hepatic enzymes immaturity (Elkomy et al. 2016; Cravero et al. 2019).

It is very difficult to link morphine function to a single gene. To understand the function of morphine in relation to one's genetic, it should be followed from the times that enters the circulation to the effect site. After intravenous injection of morphine, it is first metabolized in the liver. Glucuronidation is the major pathway of morphine metabolism. A change in UDGT (uridine diphosphate glycosyl transferase) can increase morphine glucuronidation and reduce its effect. To enter the brain cells, cassette transporter (ABBC1) is necessary. Investigations in the transporter polymorphism is in its infancy. However, it has been shown up to know that, polymorphism of the transporter can increase morphine dose up to twice. The effect site of morphine and other opioids is the μ receptor. OPRM1 gene encodes this receptor and A118G polymorphism results in reduced opioid sensitivity. Opioids, in order to be effective, must send a signal from μ receptor to brain and activate the analgesic effect. This internal signal is β Arrestin. C8622T polymorphism encodes β Arrestin, and increases morphine efficacy. The interaction of these four target sites is very complex and further research is needed in the future to clarify the relation between drug signal relationship and receptor (Galinkin et al. 2010; Kaye et al. 2019).

Hypnotics

Inhalation agents such as isoflurane are widely used in pediatric anesthesia maintenance. Anesthesia maintenance with desflurane is an effective agent with rapid recovery due to lower blood-gas and tissue-blood solubility compared to the other common anesthetics, but it isn't approved for induction and maintenance of anesthesia in non-intubated pediatric patients. The incidence of respiratory adverse

events, including coughing, laryngospasm and secretions is significantly higher with desflurane (Kapoor and Vakamudi 2012; Khan and Liu 2020).

Effect of these agents on neuronal apoptosis in different doses and duration of administration has been studied. Various studies have shown long term exposure to isoflurane can induce behavioral and cognitive impairment (Coleman et al. 2017; Demirgan et al. 2019). Neuroapoptosis will be discussed later.

MAC (minimum alveolar concentration) of inhalation anesthetics is age dependent. MAC rises during the neonatal period, peaking in infancy and then decreases throughout life (Nickalls and Mapleson 2003). Studies have shown inhalation anesthetics resistance in redheads. Melanocortin1 receptors are members of the rhodopsin family of 7-transmembrane G protein-coupled receptors. MC1R (melanocortin1 receptor) is associated with pigmentation genetics. MC1R gene polymorphism is associated with the increase of the required dose of desflurane. This mutation occurs more frequently in redheads (Liem et al. 2004). Less than 5% of inhaled anesthetics is metabolized in the body and the elimination is through the lungs. Inhalation anesthetics are also metabolized by CYP2E1. This elimination is trivial. 20–50% of halothane, 2% of sevoflurane, less than 1% of isoflurane and 0.1% of desflurane are metabolized by CYP. Genetic variations of this enzyme have no significant clinical effect (Nair 2019).

N2O is the oldest and also the most common anesthetic used worldwide. It is an adjunct to other agents during induction and maintenance of anesthesia. Nitrous oxide increases plasma homocysteine via vitaminB_{12} irreversible inactivation. It seems an acute elevation in homocysteine appears to increase the risk of cardiac complication such as ischemia (Nagele et al. 2013). C677T or A1298C variant homozygote patients for MTHFR (methylene tetrahydrofolate reductase) gene, have higher levels of homocysteine after N2O administration. Nitrous oxide administration is very dangerous and has severe complications among MTHFR deficient children. N2O is not metabolized and irreversibly oxidizes vitamin B12 in these patients. Vitamin B12 is essential for methionine synthetase function. The active form of methionine, s-adenosylmethionine, is critical for methylation in many biochemical reactions, neurotransmission, and DNA synthesis. Two infant deaths following anesthesia with nitrous due to preoperative undiagnosed MTHFR have been reported. This diagnosis should be warranted in infants with clinical symptoms e.g. hypotonia, seizure, and psychomotor retardation. 29 mutations of MTHFR are associated with methionine severe deficiency (Selzer et al. 2003).

Local Anesthetics

Regional and neuraxial blocks have many advantages in pediatric anesthesia, such as reduction of the anesthetic agent requirement and better postoperative experience for children and their parents. The quality of these blocks depends on the dose and characteristics of the used local anesthetic and site of the effect. In several cases, despite the ideal block condition, the response to local anesthetics is inadequate. Local anesthetics can act by blocking sodium channels. Resistance to local

anesthetics is uncommon. It is assumed that LA resistance is related to variations in voltage gated sodium channels (NaV). In this regard, through one family whole-exome sequencing, a genetic variant was identified in NaV. A572D mutation in SCN5A gene, which encodes NaV1.5. More incidence of local anesthetic resistance has been reported in Ehlers-Danlos syndrome with unknown cause. Further research is needed (Batas et al. 2007; Clendenen et al. 2016; Schubart et al. 2019).

NaV plays an important role in action potential formation in neurons and muscle cells. Mutation in NaV1.7 encoding gene, SCN9A, is associated with pain perception disorders such as congenital analgesia, paroxysmal pain disorder, and primary erythermalgia. Also, NaV mutations is responsible for some genetic epileptic syndromes (Catterall et al. 2010; Marković et al. 2015).

Intraoperative Awareness

Occasionally, despite the administration of a sufficient dose of anesthetic drugs during operation; the patient experiences awareness, and this is so unpleasant. Few genetic variants may be involved in intraoperative awakening and inadequate explicit memory suppression during anesthesia. Studies have found no gene having a strong association with intraoperative awareness. The authors identified 29 genetic variants in these patients including CACNA1A, CACNA1S variations, and genes encoding calcium and purinergic receptors (Sleigh et al. 2019).

Antagonists of Neuromuscular Blockers

Neostigmine is the most widely used anticholinesterase for nondepolarizing muscle relaxant reverse. It reduces the risk of residual paralysis and associated adverse respiratory events. Neostigmine has many benefits including the ability to reverse all nondepolarizing muscle relaxants, low cost and availability. A lower dose of neostigmine is required in children compared to adults, due to neuromuscular junction differences: The number and quantity of nicotinic receptors, amount of acetylcholine reserve and acetylcholinesterase enzyme activity (Wu et al. 2014; Luo et al. 2018).

Postoperative Care, Traditional and Personalized Approach

Post Anesthesia Care Unit for Stable Patients

The patients are transferred to post anesthetic care unit after deep or awake extubation (according to patients' situation). Post anesthesia care period is a high-risk time for pediatrics. Oxygen desaturation, nausea, vomiting, temperature instability may be occurred. Recovery time varies widely among different patients, (Jain et al. 2018)

Anesthesia recovery may have a presynaptic mechanism. Similar patients do not have similar recovery times. Synaxin-1A is a protein encoded by STX1A gene. Synaptic vesicles store neurotransmitters that are released during calcium-regulated exocytosis. The specificity of neurotransmitter release requires the localization of both synaptic vesicles and calcium channels to the presynaptic active zone. Syntaxin acts in this vesicle process and plays a key role in neurotransmitter release. Mutation in STX1A gene have influences on the anesthesia effect in vitro and in vivo. This mutation facilitates isoflurane recovery in Drosophila melanogaster and resistance to volatile anesthetics and intravenous anesthetic drugs (Troup et al. 2019; Templeton et al. 2019).

Emergence agitation is a common complication immediately after waking in preschool pediatric patients, and happens more with sevoflurane anesthesia. Although it is self-limited, it can be associated with severe complications such as self-injury, pulling out of intravenous line or fully (Templeton et al. 2019). In addition, there is a need for more sedative and anxiolytic drugs that prolongs recovery time in children. Also, the exact mechanism is not clear. Some studies have shown that midazolam, which its target effect site is $GABA_A\gamma_2$ subunit, reduces emergence agitation, and flumazenil reverses this effect; however, this is a controversy issue. It may be $GABR_2$ genetic polymorphism involved in emergence agitation development. A study conducted on pre-school children who underwent tonsillectomy, showed genetic polymorphism, SNP (single nucleotide polymorphism) 211037C/T, nucleotide position 3145 in intron A (G) may affect incidence and intensity of emergence agitation through GABA receptor function (Araki et al. 2005; Park et al. 2008).

PONV

Postoperative nausea and vomiting (PONV) is the most common complication of anesthesia in children. PONV incidence in this group of age is twice that of adults. Predictive factors include: age of 3 years, positive family history of PONV, history of motion sickness, type of surgery such as strabismus and adenotonsillectomy, duration of surgery equal to 30 min, opioid administration (Wiesmann et al. 2015; Chau et al. 2017).

For prophylaxis against PONV, intravenous serotonin receptor (5-HT3) antagonists such as ondansetron and granisetron given intraoperatively. 5HT3 antagonists are highly effective in prophylaxis and treatment of PONV with minor adverse effects. The other drugs such as intravenous dexamethasone decrease the incidence of PONV (Gan et al. 2014; Frelich et al. 2018). However, prophylaxis and treatment failure with ondansetron is sometimes observed. Individual variations in response to treatment is multifactorial. One of the possible mechanisms is ultra-rapid metabolism via CYP450 system especially CYP2D6 enzyme. The patients with multiple copies of the CYP2D6 allele, are ultra-rapid metabolizers and have higher incidence of treatment failure. The receptors that may play a role in PONV incidence are 5HT3B, dopamine type 2 and mu-opioid receptor. Preoperative polymerase chain reaction (PCR) and restriction length polymorphism (RFLP) test can define

CYP2D6 allele genotype (Candiotti et al. 2005; Wesmiller et al. 2013; Niewinski et al. 2018; Zhou et al. 2018a; Awad et al. 2019).

Postoperative Care in Critical Patients

Inflammation and sepsis are one of the causes leading to death in critically ill patients during perioperative period. Epigenetic modifications such as DNA methylation, histone modification and miRNAs are emerging as important players in modulating the immune responses and inflammation that ultimately result in multi organ failure in critical ill patients. Using the biomarkers for early detection of organ damage and overall prognosis is a new idea. Therapeutic strategies targeting epigenetic mechanisms are very interesting and still at early stages. Identification of epigenetic changes in personalized therapeutic approach, with the aim of using precise treatments, can improve critical care in the future. Several studies have shown that miRNAs are involved in adaptive immune response regulation and dynamically modulate the proliferation, differentiation, and the function of immune cells. Depending on the target gene, miRNAs can ameliorate proinflammatory or anti-inflammatory responses, so miRNAs exacerbate or decrease inflammatory responses (Fazi et al. 2005; Boldin et al. 2011).

MiRNA223 modifies innate immune response in two levels. It directly controls granulocytes differentiation and maturation, in addition to regulating granulocytes function (Fazi et al. 2007).

Caspase1 enzyme regulates IL_8 level, and plays a role in inflammation and apoptosis. NLRP3 is a multiprotein complex, which senses cellular stress and mediates inflammatory responses. NLRP3 is an important caspase1 regulator. NLRP3 play a role in pathogens of hereditary cryoprinopathies (a spectrum of auto inflammatory syndromes), and is associated with some disease such as gout, DM_{II}, and atherosclerosis. MiRNA223 suppresses NLRP3 through 3′UTR, thus restricts auto inflammatory processes. MiRNA223 deletion, increases susceptibility to infection in mice (Bauernfeind et al. 2012).

Postoperative *pulmonary complications* such as acute respiratory distress syndrome (ARDS) and ventilator associated pneumonia (VAP) are associated with high mortality and morbidity rate. These patients are managed by various treatments such as antibiotic therapy and lung protective ventilation strategies. In several studies, the effect of intravenous administration of selenium has been investigated with the aim of modulating inflammatory responses to ARDS. Selenium can reduce inflammatory responses in pneumonia, and significantly improve the respiratory mechanics; however, it has no effect on patient's survival (Trivedi et al. 2017; Mahmoodpoor et al. 2018, 2019a).

In order to ventilator associated pneumonia prophylaxis, administration of probiotics has been investigated in adults and children. Probiotics contain non-pathogenic flora that compete with pathogens and modulate the local and systemic immune system. Probiotic administration is a novel intervention for VAP and other

nosocomial infections prophylaxis, and especially in children can decrease VAP incidence and ICU and hospital stay (Mahmoodpoor et al. 2019a).

After major surgeries, especially open-heart surgery in children, *acute kidney injury* can increase mortality and morbidity. Clinicians try to prevent this complication by keeping stability of hemodynamic and maintaining fluid and acid-base balance in these patients. Also, early diagnosis and intervention are critical in this case. We need biomarkers for early detection of postoperative acute kidney injury, because serum creatinine is a delayed biomarker. In recent years, protein biomarkers have been investigated and used for this purpose. Three proteins including: $\alpha_1$acid glycoprotein, urinary $\alpha_1$microglubuline, and albumin can detect early acute kidney injury, which are also useful in determining the prognosis and the length of hospital stay (Devarajan et al. 2010; Greenberg and Parikh 2017).

Various studies have shown the role of inflammatory biomarkers, especially IL_8, to evaluate treatment response in patients with acute kidney injury. Serum CysC (sCys C), Serum neutrophil gelatinase lipocalin (s NGAL), Urine neutrophil gelatinase lipocalin (s NGAL), Urine liver fatty acid binding protein (UL-FABP), and Urine kidney injury molecules (UKIM) have been used to predict AKI and its severity after cardiopulmonary bypass in children (Peco-Antic et al. 2013; Greenberg et al. 2018).

Pediatric Personalized Pain Management

The progression of fields such as epigenetics, proteomics, transcriptomics, and metabolomics, has enhanced our appreciation of the complexity of acute, chronic and neuropathic pain response and its relation to individual genetic. Omics studies are relatively limited in the field of children's pain. The most prominent clinical cases in children include different responses to codeine. *Codeine* is a prodrug that converts to its active metabolites, morphine, and morphine 6-glucoronide in the liver. Most of the administrated codeine is converted to inactive metabolites by glucuronidation and N-demethylation and 10–20% of codeine metabolizes to active metabolites by CYP2D6 (Cytochrome P450 2D6) enzyme (Fig. 7.2). CYP2D6 gene is highly polymorphic with more than 100 CYP2D6 different alleles. Alleles are characterized as normal function (wild type), reduced function, and non-functional. Patients are divided into poor, intermediate, extensive, and ultra-rapid metabolizer in terms of the enzyme activity score. In poor metabolizers, activity score is lower than 0.5 and patients with activity score between 0.5 and 1 are considered intermediate metabolizer, those between 1.0 and 2.0 are extensive metabolizer and those with score greater than 2 are ultra-rapid metabolizers. In poor metabolizer patients, codeine has no analgesic effect, whereas ultra-rapid metabolizers are at high risk of serious adverse effect such as respiratory depression. There are allele's variations between racial and ethnic groups. Normal function alleles (wild type) are more frequent among European Caucasians compared to Asian and African-Americans. Genetic studies conducted on East Africa population showed that 29% of studied

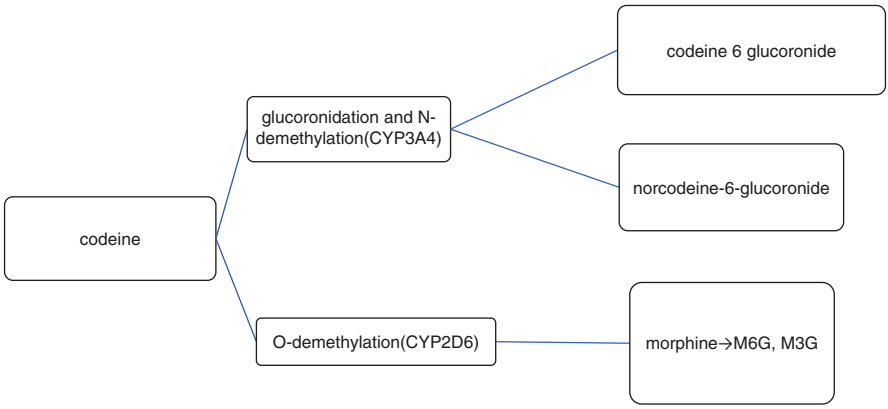

Fig. 7.2 Codeine metabolism. 10–20% of codeine converts to active metabolites by CYP2D6

subjects are ultra-rapid metabolizer and susceptible to serious adverse complications. Over the past years, several cases of respiratory depression, anoxic brain injury, and even death in pediatric patients who received appropriate doses of codeine has been reported, especially in post tonsillectomy analgesia administration. A case of infant death due to codeine consumption by the breast feeding, ultra-rapid metabolizer mother has been reported. In this regard, FDA warned of codeine use in nursing mothers due to the risk of neonatal deaths. In 2013 the use of codeine for post tonsillectomy analgesia was contraindicated in children, and in 2017, codeine and tramadol were banned in children under 12. In addition to codeine; tramadol, hydrocodone, and oxycodone are metabolized by CYP2D6 and affected by polymorphism of this gene (Aklillu et al. 2002; Bradford 2002; Thorn et al. 2009; Crews et al. 2014; Mele and Goldschmidt 2017).

Although routine preoperative genotyping is only performed in a limited number of centers, CYP2D6 pharmacogenetics can be used as a guideline for treatment of opioid use in children, especially in certain groups such as sickle cell patients, which codeine is one of the most commonly used drugs (Gammal et al. 2016; Chidambaran et al. 2017a).

Most studies among pediatric patients have focused on investigating genetic polymorphism in genes related to *morphine* metabolism, transport across membranes, and effector sites; and interesting results have been achieved (Table 7.2) Morphine is metabolized in the liver by Uridine diphosphate glucuronyl transferase. The uridine glucuronyl transferase (UGT) enzymes are subdivided into 4 families, and each of these can be categorized into subfamilies. The UGT2B7 isoform of the UGT2 family is the principle isoform responsible for morphine metabolism. Morphine is metabolized to morphine 6 glucuronide (M6G) and morphine 3 glucuronide (M3G). In patients with UGT2B7 variant in position-79 M6G/morphine and M3G/morphine ratio reduced, compared to non-carriers (De Gregori et al. 2016; Talebi et al. 2017). Studies regarding the effects of UGT2B7 on morphine glucuronidation activity are limited, and it is not clear how its genetic variant affects

Table 7.2 Genes that their polymorphism affects pharmacokinetic of morphine in children

Gene	Protein action	Polymorphism effect
UGT2B7	Morphine metabolism	Variations in the effect of morphine
ABCB1(MDR1)	Drug transporter at the BBB	Greater risk of respiratory depression
OCT1	Hepatic uptake transporter	Lower morphine clearance
ABCC3	Efflux M6G and M3G into the blood	Higher M6G plasma level
OPRM1	μ opioid receptor	Poor response to morphine

morphine metabolism. In adult studies, polymorphism of this gene has been associated with variations in clearance of morphine. Morphine is common opioid for post-operative pain management, and despite its long history of use, there is still no concordance between dose and analgesic effect in adult and children. It is used in various forms, and respiratory depression, post-operative nausea, and vomiting are its common complications. Other genes including gene coding for transport proteins such as ATP binding cassette, subfamily B, member 1(ABCB1), which is a transporter in the blood brain barrier and organic cationic transporter 1 (OCT1), which functions as a hepatic uptake transporter. ABCC3 facilitate hepatic morphine metabolites efflux. In children with rs4148412AA and rs4973665CC genotype, the likelihood of respiratory depression and long-term ICU is increasing. The effect of ABCB1 genetic variations on respiratory depression after intravenous morphine administration has also been demonstrated in children. Children with GG and GA genotype of ABCB1 polymorphism rs9282564, have a greater risk of respiratory depression (Sadhasivam et al. 2015) The efflux of morphine glucuronide from the hepatocyte cell is an ATP dependent process, mediated by ATP binding cassette transporter including ABCC3. In some literatures, the authors have demonstrated that ABBC3 gene variants contribute to variability in morphine, M6G and M3G pharmacokinetics and can potentially affect serious adverse effects of morphine. The presence of allele A at rs4148412 and allele G at rs729923 increase the risk of prolonged respiratory depression and PACU stay after pediatric tonsillectomy (Venkatasubramanian et al. 2014; Chidambaran et al. 2017a).

Organic cationic transporter (OCT) can transport morphine from blood to hepatocytes. OCT1 polymorphism causes higher risk of respiratory depression and PONV after morphine administration. Pharmacokinetic studies among pediatric patients of diverse racial and ethnic backgrounds have shown differences in morphine administration side effects. Caucasian and AA children significantly differ in the incidence of obstructive sleep apnea and total morphine use. A study on Caucasian and African American children showed association between OCT1 gene polymorphisms and the presence of side effects in Caucasian children. OCT1 polymorphism rs12208357 was associated with post-operative nausea and vomiting (PONV) and prolonged PACU stay. A significant association was also found, between rs72552763 GAT deletion and high incidence of respiratory depression (Balyan et al. 2017).

Studies showed that polymorphism of OPRM1 gene (the gene coding for mu opioid receptor type1) was associated with pain sensitivity. An association between

the A118G single nucleotide polymorphism in the OPRM1 gene and pain sensitivity was reported in children who carry the G-allele have higher postoperative pain scores (Table 7.2) (Lee et al. 2016).

Nonsteroidal anti-inflammatory drugs (NSAIDS) prevents prostaglandin production and decrease of peripheral pain and inflammation. NAIDS use as a part of multimodal analgesia. Most of NSAIDS are metabolized by CYP450 enzymes, including CYP2C8 and CYP2C9. The patients with CYP2C8*2,*3, CYP2D9*2 or *3, are poor metabolizers. The recommended treatment start dose for these patients, is half the normal dose to avoid adverse effects such as bleeding, cardiovascular or gastrointestinal events (Wyatt et al. 2012).

Acetaminophen is widely used in pediatric practice. It metabolizes in the liver extensively by glucuronosyltransferase (UGT), cytochrome P(CYP), sulfotransferases(SULT) and glutathione-s-transferase(GST). Polymorphisms of these enzymes can cause individual differences in the response to acetaminophen administration (Krasniak et al. 2014; Awad et al. 2019).

Epigenetic changes do not affect or alter DNA sequence. DNA methylation is one of the epigenetic mechanisms, which occurs in OPRM1 gene in chronic pain patients, which is correlated with increased chronic pain score, suggesting that opioids may improve pain through a direct effect on DNA transcription (Chidambaran et al. 2017a).

Toll like receptors are the members of the pattern recognition receptor (PRR) family, which play a critical role in innate immune system and their main function is to identify pathogen molecules and initiate an immune response against them; therefore, they are involved in various physiologic and pathologic processes such as septic shock. MD-2 is a glycoprotein required for response to lipopolysaccharides, which binds to LPS and extracellular domain of TLR4; therefore, it is essential for TLR4 activation. TLR4 is widely present in the cell surface and endosomes of immune and nonimmune cells, especially in human nervous system. Recent studies indicated a fundamental role of TLR4 in several chronic neuropathic pain model. Peripheral nerve injury can induce spinal microglia/astrocyte activation, so inhibition of TLR4 can develop less neuropathic pain and decrease expression of pain related cytokines. In this regard, FDA approved TLR4 inhibitors were investigated, and the authors demonstrated that these drugs can be considered as a good choice for further in-vitro and in-vivo neuropathic pain studies (Bagheri et al. 2016; Sezari 2017; Zali et al. 2019).

Gene expression leading to protein production in multiple studies of pain in rat was examined. CCL2 and Reg3b genes are correlated to the protein's monocyte chemoattractant protein 1 and pancreatic-associated protein. These proteins can be used as biomarkers of pain response in rats (LaCroix-Fralish et al. 2011).

Among the metabolite examined in rats' chronic pain, it was found that endogenous metabolite N, N-dimethyl sphingosine (DMS) production (a catabolite of ceramide) was significantly altered. DMS was intrathecally injected into healthy rats. Within 24 hours, rats developed persistent allodynia, so DMS inhibition can be considered as a novel target for reduction of neuropathic pain. Metabolomics are potential for developing new drugs and therapeutics in chronic pain (Patti et al. 2012).

TAOK3 gene encodes serine/threonine protein kinase and TAO3, an amino acid protein. TAO3 is a member of the large mammalian kinase family that is present in the cytoplasm and cell membrane, which is similar to regulating pain and analgesia proteins. Mu-opioid receptor (MOR) is an opioid receptor plays an important role in the effectiveness of opioids, especially morphine. Also, MOR and TAO3 interactions are interesting. MOR has more than 15 serine/ threonine residues, available for protein kinases. TAO3 variants can alter the phosphorylation pattern of MOR and cause desensitization of this receptor and morphine resistance phenotype. Genome wide association study in a pediatric surgery center, demonstrated an association between rs795484 and rs1277441 at TAOK3 locus and total increase morphine requirement (Cook-Sather et al. 2014).

Special Considerations

Neuroapoptosis and Developing Brain

Anesthesia drugs are extensively used in infants and children for a wide range of procedures; however, little is known about their effects on the developing brain. Millions of pediatric surgeries are annually performed worldwide. In USA, 6 million children that 1.5 million of them are infants, undergo surgery each year (Loepke et al. 2009; Kodama et al. 2011; Andropoulos and Greene 2017). Normal brain development involved neurogenesis and synaptogenesis. Non-physiological exposure to various drugs and stressors such as pain, the mother separation, hypoglycemia, hypoxia, and ischemia during the critical periods of brain development, can cause neurodegeneration. Animal studies showed that anesthesia drugs can cause neurologic and cognitive adverse effects under certain conditions such as prolonged anesthesia among infants and young children. Central nervous system has not evolved at birth and continues to grow during the early postnatal years. A large volume of experimental and laboratory studies over the past decade have demonstrated the association between general anesthesia during rapid brain development and increased neuronal apoptosis and long-term complications in mice, guinea pigs or primates (Loepke et al. 2009; Kodama et al. 2011; Andropoulos and Greene 2017). Regarding, the effect of GABA agonist or NMDA antagonist drugs e.g. midazolam, ketamine, propofol, etomidate, isoflurane, sevoflurane, desflurane, and N2O has been investigated and evidence of apoptosis and synaptic dysfunction has been obtained (Sun 2010; Wang et al. 2014; Creeley 2016; Andropoulos 2018). These drugs block neuronal transmission that result in synaptic deprivation, and then intrinsic neuroapoptosis pathway is activated due to lack of neuronal stimulation. Anesthetic drugs increase mitochondrial permeability through bcl2 proteins. The B-cell lymphoma-2(BCL-2) family protein control the intrinsic apoptosis pathway. The pro-apoptotic BCL-2 proteins, BAX and BAK can commit a cell to its programmed death by permeabilizing the outer mitochondrial membrane, release of

cytochrome c into cytosol and subsequent initiation of caspase cascade. This phenomenon rapidly occurs within 2 h of anesthetic drug exposure (Zhang et al. 2010; Boscolo et al. 2012; Zhang et al. 2012; Kajimoto et al. 2014).

N2O is a NMDA antagonist drug that its neurotoxicity effect is related to increased homocysteine levels. Homocysteine can cause cell death and cognitive dysfunction (Savage and Ma 2014). The neuroprotection effect of α_2 agonists (clonidine, dexmedetomidine) has been shown in various animal studies (Laudenbach et al. 2002; Men'shanov et al. 2007; Sanders et al. 2009).

An important question facing the pediatric anesthetist is the potential neurotoxicity of anesthetic drugs. Unfortunately, translation of bench finding to bedside is limited. It is impossible to study histologic anesthetized pediatric patients; therefore, alternative approaches such as biomarkers should be used to evaluate this important issue. Also, the safest and the most effective method should be chosen for pediatric anesthesia (Levy et al. 2016). Detectable biomarkers in blood or CSF are ideal for this purpose. Biomarkers that are sensitive and elevate shortly after drug exposure are used, and out of this, $S_{100\text{-}\beta,}$ neuron specific enolase, glial fibrillary acidic protein, myelin basic protein, α_{II}-spectrin breakdown products, apolipoprotein E, and Ubiquitin (carboxyl-terminal hydrolyze isozyme L1) can assess damage severity and outcome prediction in adult and pediatric brain trauma patients. Many of these proteins have been used to determine the prognosis of other conditions e.g. neonatal hypoxic ischemic encephalopathy (Kovesdi et al. 2010; Looney et al. 2015; Zhou et al. 2016; Fani et al. 2018). Nowadays, biomarkers such as miRNAs are used in ongoing studies. In addition, the roles of genetic and epigenetic in neuroapotosis have been investigated. Epigenetic changes are heritable, which target gene expression and function without alternation in DNA sequence. Major epigenetic mechanisms include DNA methylation, histone modification, and non-coding RNAs. The epigenetic implications for susceptibility to injury and its severity are important. Epigenetic may lead to the identification of novel markers in the field of neuroapoptosis. Animal studies have shown exposure to general anesthesia during the critical period of brain development, modulates expression, and function of the cAMP-responsive element binding protein (CREB) and CREB-binding protein (CBP), which are important in the regulation of expression several genes required for memory formation. In fact, the two key transcription factors are CREB and CBP. Accordingly, their modulation results in epigenetic changes and histone hypoacetylation, and consequently causes down regulation of c-Fos and brain-derived neurotrophic factor (BDNF). Regarding, both play a critical role in neuronal formation and function (Dalla Massara et al. 2016; Wu and Zhao 2018).

MiRNA-124 can reduce isoflurane and ketamine induced neurologic disorder. Treatment with miRNA-124 agomir enhances memory capacity and resistance to apoptosis. Accordingly, it is due to brain-derived neurotrophic factor (BDNF) elevation and decreased expression of neuroapoptotic factors including cleaved-caspase3 and Bax. MiRNA24 reduces isoflurane induced neurological deficit through prevention of early growth response 1(EGR1) expression. EGR1 gene encoded EGR family of Cys_2His_2type zinc finger proteins. Several studies suggested that it plays a role

in neuronal plasticity and synaptic exocytosis (Xu et al. 2015; Dabbagh 2016; Yang et al. 2019).

miRNA137 plays an important role in ketamine induced hippocampal neurodegeneration. Excessive use of ketamine causes severe hippocampal neuron apoptosis and also long-term memory deficit. Repeated anesthesia induced the miRNA down regulation. Cell division control protein 42 (CDC42) is the molecular target of miRNA137 and drops with ketamine usage. Neuroprotective effect against anesthesia induced through miRNA137 up regulation. In this regard, lentiviruses injection of miR137-mimics and miR137-NC into cortex have neuroprotective αIn sevoflurane anesthesia, miRNA-410-3p showed neuroprotective effect through PI3K/Akt (phosphoinositide 3-kinase/ serine, threonine kinase) signaling pathway and targeting CXCR5(C-X-C motif chemokine receotor5). This pathway can be activated by many types of cellular stimuli or toxic insults, and can also regulate many fundamental cellular functions. Activated PI3K phosphorylates AKT, thereby activating it. Akt controls a number of downstream cellular processes including apoptosis, protein synthesis, metabolism, and cell cycle, by phosphorylating a range of substrates. $IL_{6,}$ TNF-$\alpha_{,}$ $IL_{1\beta}$ have increased during sevoflurane anesthesia, in contrast miRNA-410-3p agomir attenuate inflammation (Su et al. 2019).

Sevoflurane anesthesia in new-born have significant effect on hippocampal and total brain miRNA expression that occurs immediately after exposure while in adults appears in longer duration (Lin et al. 2018). Protective role of miRNA665 through PI3K/AKt signaling pathway, by targeting Insulin like growth factor2 (IGF2) has been demonstrated; therefore, it can be used as a potential target in sevoflurane induced cognitive disorder (Lu et al. 2017). In contrast, miRNA34a up regulation increases sevoflurane induced hippocampal apoptosis; therefore, miRNA-34a inhibitor may prevent sevoflurane induced apoptosis via activation of Wnt/β catenin pathway. This pathway plays an important role in neurogenesis and hippocampal neurodegenerative disorder (Jiang et al. 2014; Libro et al. 2016).

MiRNA34-a by targeting Wnt1 and inactivation of Wnt/β catenin pathway, can suppress tumor growth. This miRNA inducts down regulation of fibroblast growth factor receptor1 (FGFR1), so anesthetic apoptosis is exacerbated. MiRNA34-a inhibitor can be considered as a novel treatment for sevoflurane neuroapoptosis (Chen and Hu 2012; Zhao et al. 2018).

MiRNA 34c is involved in the Alzheimer pathogenesis, and can be increased obviously with ketamine anesthesia. Down regulation of miRNA34c activate protein kinase C-extracellular signal regulated kinase (PKC/ERK) pathway and up regulate Bcl2 protein, thus attenuate ketamine induced apoptosis. Bcl2 is localized to the outer membrane of mitochondria, where it plays an important role in promoting cellular survival and inhibiting the actions of proapoptotic proteins. The proapoptic proteins in the Bcl2 family including Bax and Bak. Bcl2 is an antiapoptotic protein (Cao et al. 2015).

MiRNA96 augment sevoflurane effect on hippocampal neurons through insulin like growth factor receptor (IGF1R) down regulation (Xu et al. 2019). MiRNA125b-5p and miRNA188-3p are related to sevoflurane induced cognitive disorder, so

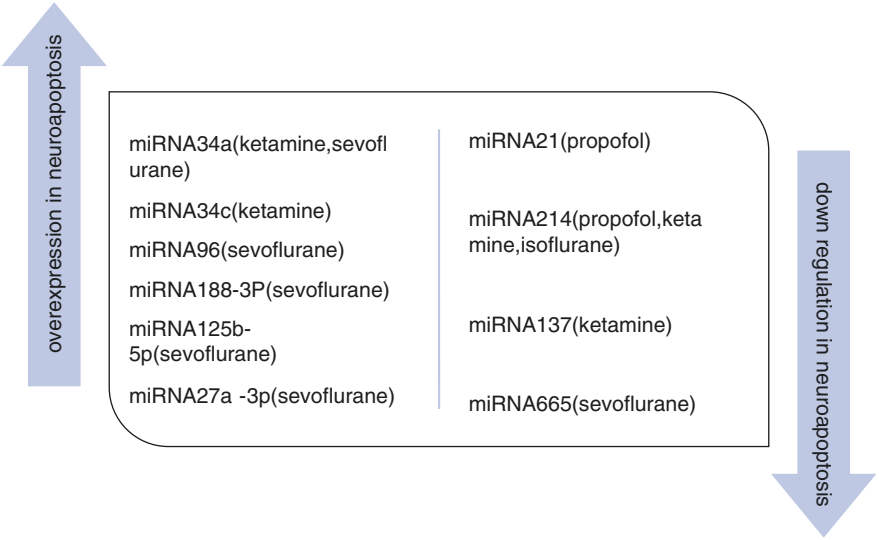

Fig. 7.3 The miRNAs alternations in anesthesia induced neuronal apoptosis

accordingly, their inhibitors can be used for apoptosis reduction. MiRNAs that affected neuroapoptosis are summarized in Fig. 7.3 (Wang et al. 2018; Xiong et al. 2019).

Anesthetic drugs induced cognitive disorder is associated with hippocampal neuroinflammation. Glycyrrhizin is used for the treatment of neurodegenerative or inflammatory diseases. It can activate hippocampal high mobility group box1 protein/ nuclear factor kappa-light-chain-enhancer of activated B cells (HMGB1/ NFKβ) signaling pathway and attenuate inflammatory cytokines and Isoflurane induced neurotoxicity. Also, it can be a potential treatment for neuroapoptosis (Wang et al. 2016a; Kong et al. 2017).

Isoflurane and other volatiles cause permanent and long-lasting changes in hippocampal proteins, similar to changes observed in Alzheimer's disease. Isoflurane induces biological processes involving synaptic plasticity, stress response, detoxification, and cytoskeleton (Kalenka et al. 2010). After exposure to isoflurane and halothane, metabolic proteins alter (Dabbagh and Rajaei 2013). Down regulation of fructose-bisphosphate aldolase and upregulation of glyceraldehyde-3-phosphate-dehydrogenase (GAPDH) and GST occur. Synaptic proteins also change, and the suggesting that synapse can act as a cellular target in anesthesia, is enhanced. Voltage dependent anion channel (VDAC) is a membrane protein that is likely to be involved as an apoptotic regulator in neurodegenerative diseases. Also, its interaction with sevoflurane can cause apoptosis.

Expression of three proteins change with both halothane and isoflurane.

- Tubulin B2A chains
- Heat shock protein cognate 71 KD

– N acetylneuraminate tidylyl transferase: It is responsible for sialoglycoprotein synthesis that is necessary for prenatal brain development and postnatal synaptogenic (Kalenka et al. 2007; Pan et al. 2008).

Ketamine and Developing Brain

Ketamine is an NMDA antagonist that is recognized as one of the potent drugs in developing brain neuroapoptosis. Many studies have been done on the effects of ketamine on the fetus and neonatal brain. The fetal and neonatal brain is sensitive to ketamine, and it has been shown that exposure for 5 h is sufficient for inducing significant neuroapoptosis. Animal studies have shown that the use of NMDA antagonists or GABA agonists by the pregnant mother in clinically dose, even single or brief exposure, can trigger neuroapoptosis. Drugs such as ethanol, phencyclidine, ketamine, N2O, barbiturates, benzodiazepines, and many of anticonvulsants and sedatives can induce apoptosis and long-term neurocognitive disorders. An animal study has shown that ketamine induced apoptosis is more diffuse and wider in fetal brain that of rhesus macaque neonates, using Activated caspase-3(AC3) immunohistochemistry, that identifies drug induced developmental neuronal death. The peak sensitivity of the fetus to NMDA antagonists is the third trimester, which is known as the development period (Zou et al. 2009; Brambrink et al. 2010; Joselyn et al. 2010; Brambrink et al. 2012).

Safety of ketamine as adjunct drug in neuraxial children block especially caudal block is in doubt. Ketamine dose used in the neuraxial block (0.5–1 mg/kg) in close to the intravenous anesthesia induction dose (2 mg/kg), and because ketamine is a lipid-soluble drug, its concentration rapidly rises in plasma and CSF, after epidural injection. In addition, animal studies have shown neuroapoptotic effect of ketamine on the spinal cord in rat neonates (Sanders et al. 2008; Lönnqvist and Walker 2012).

Glycogen synthase kinase-3β (GSK-3β) is a multifunctional enzyme that regulate neurogenesis, neuronal polarization, axon development, and synaptogenesis in developing brain. This kinase is related to neurodegenerative disorders and ketamine enhances GSK-3β induced neuroapoptosis. Ketamine decreases GSK-3β phosphorylation dependent on during of exposure. Coadministration of lithium, which is an inhibitor of GSK-3β, decreases this response (Liu et al. 2012, 2013).

Neuroprotective Agents

– Dexmedetomidine: A selective α_2 agonists attenuate sevoflurane induced cognitive disorder. Pre-treatment with dexmedetomidine is neuroprotective against volatiles and propofol in rat neonates.

Antiapoptotic expression agents, Bcl2 and PERK protein reserve by dexmedetomidine; however it is not FDA approved for neonates and children yet, and maybe causes dose dependent bradycardia and hypotension (Li et al. 2014; Wang et al. 2016a).
- Melatonin: stabilizes mitochondrial membrane and reduces apoptosis.
- Estradiol (17-β estradiol), xenon, L-Carnitine, lithium, and hypothermia are neuroprotective via various mechanisms.
- Naringenin, that is a flavonoid, can protect isoflurane induced neuroapoptosis through the regulation of PI3K/AKt pathway, decreasing inflammatory mediators and elevation of the level of antiapoptotic proteins such as Bcl2 and Bcl-xl (Hua et al. 2016).

Research on neuroapoptosis is rapidly growing and it is hoped that the results of molecular and animal studies will be applied in clinical practice.

Retinopathy of Prematurity

ROP is an eye vasoproliferative disorder affecting the premature neonates. It is one of the visual loss causes in children even in developed countries. Also, ROP pathogenesis is not fully understood. Associated environmental factors include preterm gestational age and supplemental oxygen exposure, but these factors cannot predict severity of ROP necessarily. In this case, the possible roles of other factors including genetic variants have been considered. Familial exudative vitreoretinopathy (FEVR) is an inherited disorder with clinical symptoms similar to ROP. Three genes involved in wingless/int1 (wnt) receptor signaling pathway are associated with FEVR progression. FZD4 for frizzled 4, LRP5 for low density lipoprotein receptor related protein 5, and ND for Norrie disease protein (Bizzarro et al. 2006, Hiraoka et al. 2010; Shastry 2010). The role of these genes variation in advanced ROP is demonstrated. Further studies involving genomics, transcriptomics, and proteomics are needed to obtain better understanding of the pathophysiology and management of ROP (Hiraoka et al. 2001; Kondo et al. 2013).

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Chapter 8
Personalized Anesthesia for Renal and Genitourinary System

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As an anesthesiologist when dealing with renal and genitourinary system surgeries, you would encounter two extremes of age. Pediatric group in which you should be aware of other non-urologic congenital lesions, and Geriatric group. The latter group often has concomitant respiratory and cardiovascular comorbidities. Also in both group some degree of kidney injuries is probable. Therefore, one of the most challenges and anesthesiologist encounter is preserving renal function.

10,000 years ago medicine was consisting of magic, rituals and potions whereas in 2010 genomics' decade promote healthcare to personalized medicine (Dabbagh 2020). Personalized medicine was first used by Jain in 1998 and appeared in MEDLINE in 1999 and introduced as MeSH term in 2010 as "Clinical, therapeutic and diagnostic approaches to optimal disease management based on individual variations in a patient's genetic profile". Precision medicine is the best way to merge biotechnology into medicine in order to understand pathophysiology and pharmacologic responses and patients' management (Jain 2015). In general, precision medicine can give us new point of care test, new drugs, new prognostic factors or it can give us new individualized aspects of old treatments (Dabbagh and Elyassi 2016; Dabbagh 2017; Sezari and Dabbagh 2019).

From 1846 when William Morton demonstrates first modern anesthesia in ether dome, anesthesia promotes in certain aspects. Till a generation before us anesthesia was practiced by algorithm in which weight and comorbidities were the most important factors in dosing drugs and choosing the best practice. But this approach encountered a problem, as it is obvious from definition of ED95 and MAC not all patient will benefit from this approach. Therefore, gradually a paradigm shift occurred toward individualizing our management. As it occurred in fluid

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management; in 1970s individualizing fluid management in order to achieve optimized cardiac output took place of conventional management and introduced goal-directed therapy as an individualized medicine example (Forni et al. 2017).

What Is Genomics?

Genome is defined by all of a person's gene or an organism's complete set of Deoxyribonucleic acid (DNA). Genomics is the study of genome, interactions of these genes and with the environment. As we know, every human cells contains three billion DNA base pairs that make up the human genome. DNA is the chemical compound that contains information about all of our activities. Its molecules are made of spiral and paired strands know as double helix. Each DNA strand made from four kinds of nucleotide bases; Adenine (A), Thymine (T), Guanine (G), and Cytosine (C). A always pairs with a T and C always pairs with a G. the order of these nucleotides determine the meaning of each gene.

Our DNA is stored in 23 pairs of chromosomes located in nucleus of each human cells. The sequence of DNA containing the instruction for a protein or sets of protein is called a gene. Human genome contains 20,000–25,000 genes which construct proteins as enzymes, receptors and etc.

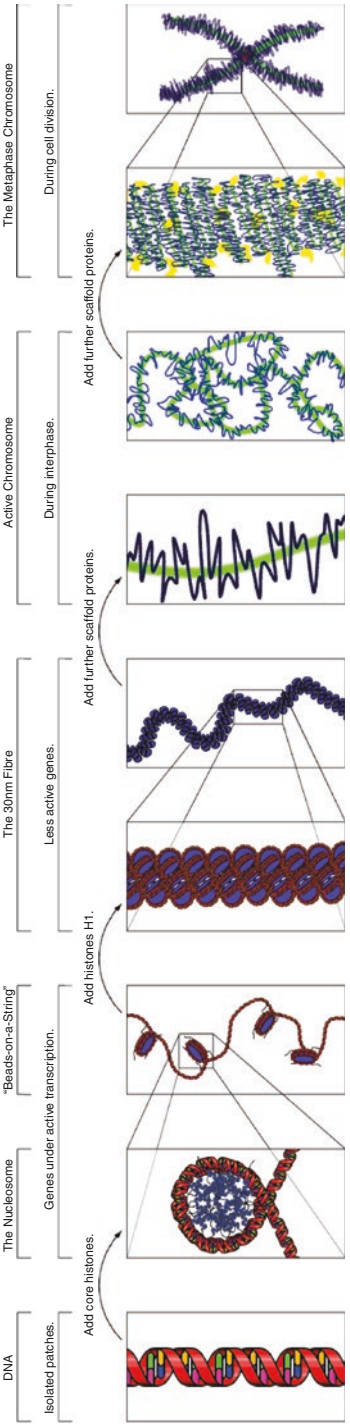
Gene's DNA is transcript by an enzyme into a molecule called messenger ribonucleic acid (mRNA). mRNA is transferred into cytoplasm in order to meet an organelle name ribosome. Ribosome link amino acids by the coding of mRNA to build a specific protein.

What Is Epigenomics?

Besides genome which is inherited totally, epigenetics that is effected by environmental factors can change expression of each gene. Epigenetics which is also heritable, do not directly change the DNA molecule but it changes the way it is expressed. As you know, all the cells of human body are composed of the same genome but it is the epigenetics that differs the cell from an epithelial cell to a white blood cell (WBC). There are two common epigenetic modifications: (1) DNA methylation (2) Chromatin remodeling.

DNA methyltraferases (DNMTs) can transfer a molecule of methyl to the DNA molecule most of the times to Cytosine. This phenomenon can alter the gene expression if it happens in promotor section of the gene. Also it plays role in genomic imprinting, X-chromosome inactivation and when dysregulated it could be related to diseases like cancer (Jin et al. 2011).

Like the thread wrapped around the spool, DNA is wrapped around eight histone protein core this action reduce the length of human genome from 1.8 m to 90 μm. Therefore, histone packed your genome in functional units called nucleosome. Chromatin which is DNA packed with proteins, could be modified in order to make a region accessible by transcriptase enzymes.



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What Is Proteomics?

In 1994, Marc Wilkins introduced "Proteomics" as a portmanteau of protein and genome. It indicates proteins which are expressed by genome. Although genome has all the information needed for an organism to live, it is static. Life is dynamic and therefore is directly related to the way genome is expressed in to proteins. Although "Human Genome Project" was an obligatory step in order to move toward cellular biology, the way genome is expressed could be a key.

In personalized medicine, proteomics plays an important role in drug discovery, representation of patient-to-patient variation and target based therapy to a specific biomarker.

What Is Metabolomics?

Like the genome which is all of a person's genes, human metabolome is the set of all metabolites in humans. Metabolomics is the study of metabolites as a chemical fingerprint which every cellular process leaves behind. As it is defined, metabolome do not include enzymes, genetic and structural materials (Jain 2015).

The Human Metabolome Database (HMDB) of Canada (http://www.hmdb.ca) is a freely accessible database containing detailed information about 114,008 metabolite entries in humans. It designed to have three kind of data: chemical, clinical and molecular data. This valuable resource could be used for application of metabolomics, clinical chemistry, biomarker discovery or general education (Wishart et al. 2018).

Also UK Biobank (http://ukbiobank.ac.uk) is a national and international resource that follows the health and well-being of 500,000 participants. Its goal is to improve the prevention, diagnosis and treatment of a wide range of diseases. They have gathered their genome and about 20 biomarkers in their database (UK Biobank 2019).

In addition to above international efforts to improve databases, National Institute of Diabetes and Digestive and Kidney Diseases (part of NIH) has launched a project named Kidney Precision Medicine Project in which aims to ethically obtain and evaluate human kidney biopsies in order to create kidney tissue atlas. (de Caestecker and Harris 2018) This project shows promising data regarding diagnosis and prognosis of AKI.

In this chapter we have gathered new developments in precision medicine regarding renal and genitourinary system which could be effective in perioperative period. In order to reach our aims, this chapter consist of three sections: pre, intra and post-operative.

Preoperative Care

Anesthesiologist's interventions often begin in the first pre-operative visit. This could be a great opportunity in order to reduce perioperative complications and modifying risk factors. One of the most important perioperative morbidities regarding renal system is Acute Kidney Injury (AKI) (McKinlay et al. 2018).

Most of the risk factors of AKI could not be modified as shown in Table 8.1. However as mentioned above, modifying risk factors is one of the aims for preoperative visit, so below interventions in this period could reduce the risk of AKI.

Since prolonged fasting could induce metabolic stress, mitochondrial dysfunction and insulin sensitivity and also these changes could increase the risk of postoperative AKI, therefore minimizing fasting in preoperative care could be beneficial (Ali Abdelhamid et al. 2016). On the other hand, fasting could induce hypovolemia which is associated with AKI. Therefore, volume expansion in preoperative period have crucial effect to protect the kidneys.

Table 8.1 Risk factors for peri-operative AI

Category	Risk factor	Comments
Demographic	Age	>65 years and neonates
	Sex	Male for non-cardiac surgery Female for cardiac surgery
	Race	African-American
Status	ICU patient	
	ASA class	AKI with higher classes
Current Pathology	Acute stress	Emergency surgery Intrathoracic surgery Intraperitoneal Surgery
	Sepsis	Lower Cr production
	Multiple Organ Failure	
	Trauma	Rhabdomyolysis
	Abdominal Hypertension	
Comorbidities	Chronic kidney disease	
	Diabetes Mellitus	
	Obesity	Metabolic Syndrome
	Peripheral vascular disease	
	Coronary Artery Disease	
	Heart Failure	
	Hypertension	
	COPD	
	Liver disease	
	Anemia	Transfusion risk

Adapted from McKinlay et al. (2018) and Garwood (2015)

In addition to maintaining euvolemia, preoperative hemodynamic optimization can reduce postoperative AKI. This optimization could be reached with the aid of invasive monitoring of cardiac index, systemic vascular resistance, Delivery of O_2 or FT_c (Brienza et al. 2009).

Exposure to the contrast media could cause contrast-induced nephropathy. As many patients require contrast enhanced imaging prior to surgery, it has been advised to delay surgery for at least 3 days after contrast exposure (Garwood 2015).

Preoperative hemoglobin level (Hb) is of paramount importance. It has been shown that Hb between 10.1 and 12 mg/dl could double the risk of AKI and levels below 10 mg/dl could quadruple that rate. It should be noticed that could also increase the risk of AKI therefore strategies rather than transfusion should be used in order to increase Hb level (Garwood 2015).

Another intervention to minimize the risk of AKI in preoperative period is discontinuing nephrotoxic medications. It has been thought that Angiotensin-Converting Enzyme Inhibitors (ACE-I) and Angiotensin Receptor Blockers (ARB) may cause intraoperative hypotension and decrease glomerular perfusion pressure therefore it has been advised that these medications should be discontinued 24 h before performing surgery. In contrast, new studies could not demonstrate this phenomenon and advised that the decision should be individualized regarding type of surgery, cardiac and renal comorbidities (Zou et al. 2016; Hollmann et al. 2018). Non-Steroidal Anti-Inflammatory agents (NSAIDs) are also known for inducing AKI, therefore the use of them should be balanced against their potential for AKI (McKinlay et al. 2018). Also statins therapy in preoperative period has been shown to reduce postoperative AKI (Oh et al. 2018).

One the most common developmental diseases is Congenital anomalies of the kidney and urinary tract (CAKUT). CAKUT is responsible for up to 40% of dialysis in childhood and young adults. So far modeling for these diseases could be divided into two groups; In vitro proteomics studies and In vivo models. Stable cell culture systems have been proposed in order to investigate mutations leading to CAKUT and so far kidney-derived cells including, mpkCCD, HEK 293, MDCK and IMCD3 are widely used. It has been shown that mutations affecting transcription factors like HNF1B, PAX2, or TBX18 may cause these anomalies. Also pathways like GDNF-RET have been sough using in vitro modeling methods. However, these methods could not define different cell types or whole-organ level. So other methods have been proposed. As mice metanephrones are similar to humans, they have been studied to find genes involving in CAKUT like Islet1 or ITGA8. Also models of ex vivo murine kidney and zebrafish have been studied in order to find specific genes affecting this conditions (van de Hoek et al. 2015). Kohl et al. (2016) by targeting 96 microRNA in 1213 individuals showed more than 30 known monogenic cause fail to explain 70–80% of cases. Although most of these innovations are not yet clinically applicable, it can be estimated that in the future, by using point-of-care tests you can find the association of CAKUT with other organ malformations regarding anesthesia (Dabbagh and Elyassi 2016; Dabbagh 2017).

On the other hand, prematurity and preterm labor is accompanied major complications and heavy economic burden. One of the consequences is abnormal kidney

function. Assessment of renal function in newborns is associated with numerous difficulty so far increases in creatinine and urea and decrease in sodium and osmolality has been shown to be correlated with renal maturation. In addition, elevated amniotic Cystatin C is thought to be a marker of obstructive uropathies (Joshi et al. 2017).

Intraoperative Care

One of the most important concerns about kidneys by anesthesiologist is occurrence of AKI in perioperative period. Although its incidence is reported to be only 1–6%, the mortality rate would be 42% which elucidate the importance (Yuan et al. 2018; Gumbert et al. 2020).

Cardiovascular

Hypotension is an independent risk factor regarding postoperative AKI, so avoiding perioperative hemodynamic instability would be one the most important protective strategies. It has been studied that hypotension as defined by mean arterial pressure (MAP) < 55 mmHg for more than 20 min have a relative risk of 1.5 for AKI (McKinlay et al. 2018). IV fluids, vasopressors and inotropes could be used when encountering intraoperative hypotension. None of them has been shown to be superior to the others. One of the best solutions for treating hypotension would be goal directed therapy (GDT) which respect the individual itself. One of the strategies in this approach is by determining stoke volume (SV) and oxygen delivery index (DO_2I). In this approach if SV increased by 10% by fluid challenge (infusion of 500^{cc} colloid in 20 min) then fluid challenge would be repeated and if it decrease by 10% through operation fluid challenge would be repeated also decrease od DO_2I to less than 600 ml/min/m^2 would suggest using inotrope (Bartha et al. 2016). Another strategy would be judicious use of vasopressor as they both improve renal blood flow and increase renal artery resistance.

Respiratory

The impact of hypoxia and hypercarbia due to hypoventilation is not questionable in occurrence of AKI due to decrease in oxygen delivery and systematic vasoconstriction. Recently it has been suggested that mechanical ventilation per se could also be a risk factor for AKI with three-fold increase in odds of occurrence. (van den Akker et al. 2013). Although this finding could not be generalized due to heterogeneity in trials, it would be a wise choice to apply lung protective strategy (6 cc/kg

tidal volume, using optimal PEEP, and determining respiratory rate by measuring end tidal CO_2 or $PaCO_2$) for all the intubated patients. Also controlling Acid-Base balance during anesthesia has been shown to reduce specific cytokines hence more studies are needed (Fathi et al. 2018).

Anesthetic Technique

As far as we know, the association of renal impairment and anesthesia techniques has not yet described well. Although the renal toxicity of methoxyflurane has well understood, other volatile agents including sevoflurane, do not have this effect. Moreover, recent studies described their protective profiles with preconditioning effect. National Surgical Quality Improvement Program (NSQIP) conducted a meta-analysis of its database by comparing more than 300,000 cases regarding effect of anesthesia type on postoperative mortality and morbidities. This study also showed no beneficial effect of one technique to the other (McKinlay et al. 2018). On the other hand in specific surgeries like total knee arthroplasty, spinal anesthesia has been showed to have beneficial outcomes and also lower postoperative AKI (Kim et al. 2019).

Glycemic Control

Although tight control of glucose is no longer recommended for all of diabetic patients, it has been shown that sustained hyperglycemia and rapid alteration in blood glucose level are both risk factors for AKI. Therefore, it is recommended to maintain glucose level below 200 throughout the operation in order to protect body from its complications (McKinlay et al. 2018).

Musculoskeletal

Although rhabdomyolysis during anesthesia is a very rare condition, this phenomenon has been reported in prolonged surgeries (Grammer et al. 2018), Propofol infusion syndrome (Kam and Cardone 2007), use of tourniquet (Turkmen et al. 2015), and compartment syndrome. Also it is a common complication following malignant hyperthermia. Prolonged surgeries, Morbid obesity, hypotensive anesthesia and tourniquet use are risk factors for occurrence of rhabdomyolysis (McKinlay et al. 2018). As other causes of rhabdomyolysis, early diagnosis and early intervention could reduce the morbidity and mortality following this phenomenon.

Pharmaceutical Agents

It has been traditionally accepted that some drugs could have renal protection properties which include but not limited to dopamine, dopamine analogies, diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitor drugs, N-acetyl cysteine, sodium bicarbonate, antioxidants, erythropoietin and IV fluid administration. Although these could be beneficial in some circumstances but recent studied found a significant heterogeneity in outcomes and failed renal protection in some cases (Zacharias et al. 2013).

Recent developments have targeted molecular pathways in order to surmount this heterogeneity. RenalRIP trial showed that Remote ischemic preconditioning (RIPC) could be a good pathway to protect kidneys in short-term and long-term (Jamshidi et al. 2016; Zarbock et al. 2017). Based on this hypothesis several investigations have been done in order to find targets to intervene. As an organ is faced to hypoxia, the response would be producing hypoxia-inducible factors also known as HIFs. Therefore, perioperative induction of HIFs could be a pathway to protect kidneys against deferent insults. These inducers like dimethyloxaloylglycine (DMOG) and TRC160334 have been studied in this field (Yuan et al. 2018). By considering epigenetics in this hypothesis, HIFs have been shown to upregulate microRNA-21 at transcriptional level which would open new horizons for investigations (Crimi et al. 2019).

Postoperative Care

In the post-operative period, complications like hemorrhage, sepsis, cardiac failure, rhabdomyolysis, intra-abdominal hypertension and compartment syndrome could be triggers for AKI. Therefore, close monitoring in order to maintain renal perfusion pressure and euvolemia is the golden key to manage postoperative AKI. It should always be remembered that postoperative oliguria could be a cause of dehydration or stress response to pain, trauma or surgery. So liberal use of diuretics without assurance of maintaining euvolemia could induce renal impairment.

Biomarkers

The term “Biomarker” is a coinage of biological and marker, in 1998 the National Institutes of Health Biomarkers Definitions Working Group defined it as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.” Through history its definitions get broader through which Who defines it as “almost any measurement reflecting an interaction between a biological

system and a potential hazard, which may be chemical, physical, or biological. The measured response may be functional and physiological, biochemical at the cellular level, or a molecular interaction." (Strimbu and Tavel 2010) so biomarkers could be classified in three categories: those that define patient's disease (diagnostic biomarkers), those that predict patient's response to therapy (prognostic biomarkers), those that predict patient's long term outcomes (prognostic biomarkers) (Mariani and Kretzler 2015).

One of the reasons of which diagnosis of post-operative AKI is delayed and therefore its prognosis would be affected is the fact that its diagnosis is based on serum creatinine. So it has long been researched to find another possible indicator of AKI in order to make diagnosis it earlier. One of the possible replacements is biomarkers (Schaub and Heung 2019).

Numerous biomarkers are proposed for early detection and causal relationships for AKI. For instance, Tissue Inhibitor of Metalloproteinase-2 and Insulin Growth Factor Bind Protein-7 (TIMP2*IGFBP7) which are biomarker of cell cycle arrest may describe a pathway by which is activated by many insults in kidneys. Also, KIM-1 could be a response of kidneys to nephrotoxins (Forni et al. 2017). Neutrophil Gelatinase-Associated Lipocalin (NGAL) which could be detected in serum and urine, is also associated with AKI. NGAL shows promises in early detection of AKI specially due to sepsis (Shang and Wang 2017). Kidney Injury Molecule-1 (KIM-1) which is upregulated in proximal tubule, has been identified as a blood biomarker of kidney injury, especially when renal cells are affected by nephrotoxins (Sabbisetti et al. 2014; Song et al. 2019). A meta-analysis also proposed urinary InterLeukin-18 (IL-18) as biomarker for AKI with moderate predictive value in all clinical settings (Liu et al. 2013). Many studies also demonstrated that Human liver-type acid-binding protein (hL-FABP) could also be a promising biomarker (Xu et al. 2015). N-acetyl-β-d-glucosaminidase and α-glutathione S-transferase may also be enzymes which is detected in urine sample when renal tubular cells are damaged (Roberta and Hines 2018). β_2-Microglobulin as a traditional biomarker has also become popular again due to its cost-effective properties (Talebi et al. 2017; Barton et al. 2018).

c-AKI (congestive AKI) is a subtype of AKI mostly occurred after right ventricular dysfunction. Zelt et al. (2018) demonstrated that cardiorenal biomarkers such as hs-cTnT and NT-proBNP are potential biomarkers for c-AKI. Although they had limited sample size for generalized conclusion, the idea of specific biomarkers for different renal pathologies could be investigated in other settings like diabetic nephropathy, aminoglycoside induced nephropathy and etc.

In preclinical studies it was shown that a synthetic α-MSH agonist called ABT-719 (also known as AP214) has anti-inflammatory effect. Therefore, it had been tested in patients undergoing cardiac surgery who was high risk for developing AKI. This study does not show any significant effect on prognosis of AKI probably because there is not any melanocortin receptors in renal cells (de Caestecker and Harris 2018). So we can learn that any development in this field must be based on molecular knowledge of the process in animals and humans and also their differences.

Also biomarkers could be used in order to anticipate the natural history of AKI. For instance, Bhatraju showed that Angiopoietin-1 and Angiopoietin-2 (Ang1/Ang2) can be used in prognosis of AKI. Although Ang1 and Ang2 both acts via Tie-2 receptors, they have opposing actions: Ang1 stabilizes the vascular endothelium whilst Ang2 destabilizes it. Therefore, the ratio of these two endothelial growth factors could be an indicator of the prognosis of AKI (Schaub and Heung 2019). Another predictive biomarker is Transient Receptor Potential Ankyrin 1 (TRPA1) which is a redox-sensing Ca^{2+}-influx channel. When high level of this protein is expressed in patients with Acute Tubular Necrosis, nontotal recovery of renal function would be expected (Wu et al. 2019).

Secretory leukocyte protease inhibitor (SLPI) is an alarm anti-protease which is expressed in myeloid and other epithelial cells. This protein counteracts with granulocytes proteases in proteolytic attacks. This protein is also described to have early diagnostic role in post cardiac surgery AKI (Averdunk et al. 2019).

Chloride level is also investigated in order to be recognized as a predictive biomarker for occurrence of AKI. Although some literature proposes chloride level as a good indicator others have not defined any physiologic or clinic association between them (Yessayan et al. 2017; Marouli et al. 2018; Commereuc et al. 2019; Oh et al. 2019; Rein and Coca 2019). Therefore, further investigations could clarify the statement.

Although this approach shows promising and commercial kits are available (Fan et al. 2019), there are two major problems, one is traditional non-reproducibility because of false positive biomarker selection and the other is absence of generalizability or external validity of study populations (Sweeney and Khatri 2017).

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Chapter 9
Personalized Anesthesia for GI Tract and Hepatobiliary System

Ata Mahmoodpoor

Patients with end-stage liver disease have a high perioperative morbidity and mortality. The pharmacokinetics and pharmacodynamics of anesthetic drugs are significantly altered in liver diseases. Patients with hepatic diseases have extrahepatic problems like gastrointestinal, respiratory, cardiovascular, coagulopathy, hematological, neurological and renal problems. So, the intravascular volume, and the extra-hepatic effects of liver disease on different organs must be addressed before the surgery. Invasive monitoring is recommended during major surgeries. Close attention should be paid to the liver blood flow, renal function, encephalopathy, and prevention of sepsis (Dabbagh and Rajaei 2013; Farzanegan and Zangi 2017). The dose of thiopental and propofol should be reduced in these patients. Etomidate may be used safely but offers little advantage over thiopental. Chronic alcohol use may increase anesthetic requirements, but all IV agents should be used with great care. The metabolism of succinylcholine may be slowed because of the reduced pseudocholine esterase concentrations, but in practice this causes few problems. There is an apparent resistance to non-depolarizing neuromuscular blockers in patients with liver disease, which may be due to an increased volume of distribution or altered protein binding. Vecuronium and Rocuronium, both steroid-based NMBs, have a prolonged elimination phase in severe liver diseases. Cisatracurium may be the drug of choice but in all cases, it is advisable to monitor the neuromuscular function. It seems that remifentanil is a suitable drug for these patients and is ideally suited to intraoperative use as it is metabolized by tissue and red cell esterases, which unlike plasma esterases, are preserved in patients with severe liver disease (Chen et al. 2017). Regarding volatile anesthetics, isoflurane, sevoflurane, and

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Desflurane undergo minimal hepatic metabolism and can be regarded as safe (Dabbagh and Rajaei 2011; Mahboobi et al. 2012). Desflurane, being the least metabolized and providing the quickest emergence from anesthesia, is probably the ideal volatile agent. Abnormal liver enzyme test results may be seen in up to 4% of normal individuals and up to 36% of psychiatric patients, although the prevalence of clinically significant hepatic dysfunction in these individuals is less than 1%, suggesting that further costly preoperative testing is unnecessary in asymptomatic patients. Patients with asymptomatic elevations in serum transaminase levels (less than two times the normal values) may undergo surgery with minimal impact on perioperative outcome.

Retrospective data suggest that patients with acute hepatitis from any cause are at increased risk for hepatic failure and death after elective surgery. Thus, elective surgery should be delayed in these individuals until the resolution of the acute hepatocellular dysfunction can be confirmed. Asymptomatic patients with any form of chronic hepatitis should be carefully assessed before elective surgeries, and meticulous care should be taken to maintain hepatic perfusion in the perioperative period and to avoid any hepatotoxic drugs or significant hypotension that may result in liver failure or hepatic encephalopathy (Talebi et al. 2017). Diseases of the gastrointestinal system frequently result in abnormal gastric function, with potentially increased anesthetic risk caused by increased intragastric pressure, delayed gastric emptying, gastric dilation, and increased gastric secretion. Although volume, pH, and amount of particulate matter in the aspirate appear to be the three most important factors determining the severity of the pulmonary insult, overall medical fragility of the patient is often the most important determinant influencing the clinical course and outcome of pulmonary aspirations. Extensive bowel, pancreatic, or esophageal resections entail considerable morbidity with potential serious postoperative complications. Laparoscopy entails the installation of gas into the peritoneal cavity with physiologic changes resulting from this gas under pressure and subsequent surgical positioning. Hemodynamic compromise may occur, which, although rare, can be catastrophic. Anesthetic care of these patients is especially challenging. If the lower esophageal sphincter is not functioning properly, or if a hiatal hernia exists, stomach contents may reflux into the esophagus and pharynx during anesthesia and surgery, increasing the potential for serious aspiration pneumonia. During laparoscopy, the development of pneumothorax and/or pneumomediastinum is a serious and/or potentially life-threatening complication. Approximately 40% of the patients with gastroesophageal reflux have delayed gastric emptying, and in approximately one-third of these, the delay is clinically significant. Maneuvers necessary for a blunt esophagectomy are capable of causing serious hemodynamic and ventilatory compromise, and require appropriate monitoring of blood pressure and respiration. Bariatric surgery patients may have significant medical problems and their perioperative care can be quite challenging. Newer procedures continue to lessen both morbidity and mortality (Amornyotin 2013).

Metabolomics

The optimization of drug therapy according to the personal characteristics of patients is a perspective direction in modern medicine. One of the possible ways to achieve such personalization is through the application of "omics" technologies, including the current promising metabolomics methods (Dabbagh and Elyassi 2016; Dabbagh 2020). In the present postgenomics era, the significance of metabolomics as one of the latest "omics" areas for the assessment of drug effectiveness and toxicity has increased significantly. The utility of metabolomics in anesthesiology is not surprising. Genes and genetic risk scores can be used to indicate what might happen in terms of biochemical or cellular functions, whereas metabolic profiling and metabolic phenotyping indicate what is happening at a biochemical level. Metabolic profiling, which can simultaneously identify thousands of metabolites, has shown significant results in many scientific and clinical applications to date.

Pharmacometabolomics is a new approach based on the practical application of metabolite profiles of easily accessible biofluids. This approach can be used to predict the effectiveness of a drug prior to dosing, and to monitor the post-dose effectiveness of the medication and the disease development, thus avoiding ADR. Pharmacometabolomics is a personal approach to the therapy that achieves the goal of personalized medicine: "the right drug for the right patient at the right dose". One of the main problems of implementing Pharmacometabolomics in clinical practice is the difficulty of standardizing the metabolomics methods (Balashova et al. 2018).

The field of metabolomics is expressed as the study of small-molecular-weight molecules involved in the metabolism, with a focus on how their levels change and/or which metabolites are more involved in response to different drugs or pathologies (Chen et al. 2017). Metabolomic profiling can be applied to the spectra obtained in vitro (e.g., urine, blood, or cerebrospinal fluid) using mass spectrometry or nuclear magnetic resonance, or in vivo from the brain, using magnetic resonance spectroscopy (1 HMRS) (Chan et al. 2009). An advantage of metabolomics is its perfect ability to track multiple metabolites concurrently by a noninvasive approach in the live human or animal brain. There are a few studies regarding metabolomics in anesthesia which is a new and rapidly growing field. Makaryus et al in their work compared the metabolic profile during propofol with isoflurane anesthesia, and showed that prolonged isoflurane anesthesia was characterized by higher levels of lactate and glutamate compared to long-lasting propofol. In contrast, propofol anesthesia was characterized by very low concentrations of lactate as well as glucose. They showed that lactate was fivefold higher with isoflurane compared to propofol anesthesia and independent of lactate in blood (Makaryus et al. 2011). This finding is so important for the ones who have hepatobiliary problems or undergo these surgeries especially if they have hypoperfusion. Liu et al in their experiment showed that sevoflurane anesthesia causes significant oxidative stress, neuroapoptosis, and cellular ultrastructure damage which is associated with altered organ metabotype in

the neonatal rat. The metabolism and metabolomics of ketamine remain poorly understood. Results of a recently performed study showed that, based on the time course of their appearance and due to the low levels of ketamine registered, active metabolites are expected to be involved. Most of its effects are due to the binding of ketamine and metabolites such as norketamine and dehydronorketamine to the serum proteins, mainly albumin and a1-acid glycoprotein (Dinis-Oliveira 2017). Ghini and colleagues evaluated metabolomics profiling of pre and post anesthesia plasma samples of colorectal patients obtained via ficoll separation and showed that, samples collected during anesthesia are not suitable for metabolic profiling studies aimed at patient stratifications, because interpersonal variations are reduced by the overall depression of the metabolites' levels. On the other hand, this study showed that the plasma metabolomics might represent a valuable tool to monitor the effects of different sedatives and/or the individual metabolic responses to anesthesia, providing hints for an appropriate tuning of personalized sedation procedures (Ghini et al. 2015). Jiang et al in their study demonstrated that prenatal exposure to sevoflurane disturbs methylation and arginine/proline metabolism, which may impose adverse impacts on neurodevelopment of offspring and contribute to the neurotoxicity on offspring's generation after sevoflurane anesthesia in adult animals during pregnancy (Jiang et al. 2017).

As most of inhaled anesthetics are metabolized in liver, regulating the methylation and the arginine/proline metabolism can be as the potential therapeutic way for preventing inhalational anesthetics from impairing neurodevelopment, being very important for anesthesia during pregnancy. Jacobs with his colleagues evaluated the metabolomic differences between an inhalant and an intravenous anesthetic observed in the rodent brain and showed that isoflurane anesthesia was characterized by higher concentrations of lactate, glutamate, and glucose in comparison with propofol. They also showed a higher glucose and lactate with sevoflurane in the human brain compared to propofol, which could reflect greater neuronal activity with sevoflurane, resulting in enhanced glutamate-neurotransmitter cycling, increased glycolysis, and lactate shuttling from astrocytes to neurons or mitochondrial dysfunction. Further, the association between the emergence delirium and lactate suggests that the anesthesia-induced enhanced cortical activity in the unconscious state may interfere with rapid return to the "coherent" brain connectivity patterns, required for normal cognition upon emergence of anesthesia (Jacob et al. 2012). So in patients with liver dysfunction being at the risk for neurological disorders, like delirium or cognitive dysfunction, after the anesthesia, intravenous anesthetics may be beneficial. Emergence of anesthesia as the ending stage of anesthesia is not simply the reverse process of induction. Recent findings demonstrated that induction and emergence are partly subjected to the control of different neural pathways. Having knowledge of these mechanisms may help prevent a large percentage of anesthesia complications. Consequently, a better understanding of anesthesia emergent neurobiology could open a new era in anesthesiology, aiming to design new and safer anesthetic strategies, which can be a hot topic for metabolomics in the anesthesia practice.

The mammalian gastrointestinal tract has co-developed with a large number of microbes in a symbiotic relationship, having essential roles in health and disease. Since dysbiosis of the gut bacteria results in the alterations in the levels of certain microbial and host co-metabolites, identifying these markers could enhance the early detection of diseases. So, these metabolic fingerprints can give us clues, as to how to manipulate the microbiome to promote health, or treat diseases, and finally better manage the anesthesia and drug therapy to decrease the complications (Daliri et al. 2017).

Proteomics

Genes are the main sites of biologic information, but proteins are the main sites of biologic activity, giving proteins a unique importance. Proteomics is the study of all the proteins encoded by the genome present in specific tissues, cells, or fluids. It is not only the study of differences in protein levels, but also the study of the modifications that occur after the protein synthesis. Study of the proteome is particularly important because the levels of the mRNA often do not correspond to the levels of the protein product. Unfortunately, proteins are much more complex than DNA and RNA, in a variety of ways. Proteins are composed of 20 amino acids rather than the four nucleotides that constitute DNA and RNA. The three-dimensional structure of the proteins, which is critical to their function, usually is much more complicated than the three-dimensional structure of DNA. The complexity of proteins has slowed the development of high-throughput methods for the examination of large numbers of proteins simultaneously. Nevertheless, great progress has been made in this field and a number of new techniques are being developed to enhance the use of proteomics for studying the diseases (Stelzhammer et al. 2011).

Numerous genomic variants with demonstrated clinical utility have been identified, opening the way for their application to help individualize the drug use for optimal outcomes. As a result, the routine integration of these data to anesthesia as the individualized protocol, has the potential to reduce healthcare costs and improve patients' outcomes, safety, and satisfaction.

Futterer and colleagues in their study showed that exposure to Desflurane can alter the levels of protein expression in the organs. These included alterations in the proteins involved in cellular trafficking, mitochondrial function and signal transduction. These changes were shown to be continued until at least 72 h after the anesthesia, which emphasize that the physiological effect of the anesthetics can extend after immediate postoperative period (Fütterer et al. 2004). Proteomics expresses an ideal field for understanding of the patient specific drug responses which is important in the pharmacokinetic properties of anesthetic drugs. For example regarding pain management, physicians should know information about the individual patients' opioid receptor profile, like the density of the receptors and the response of the receptors to analgesics, to manage the best pain control protocol for each person (Birch et al. 2004). Also such information should help guide the dosing of the

neuromuscular blocking agents, which need extensive hepatic metabolism for their clearance. Screenings of the inhaled anesthetics for large pools of both soluble and membrane-associated proteins, and lipids, show important information regarding the identification of the specific sites of action. The use of proteomics can help to optimize perioperative transfusions, thus decreasing the related complications like infections, allergic reactions and transfusion related acute lung injury (Reddy and Perrotta 2004; Talebi et al. 2017).

In the future the preoperative evaluation and the risk stratification will move beyond chest radiographs, electrocardiography, and physical examination. Different samples will likely be evaluated for proteomic analysis and serum enzyme profiles. Finally, the use of proteomics methodology for solving these questions is almost certain to improve the scientific foundations of the discipline and to enhance the patient care.

It is conceivable that, in a not very distant future, the patients undergoing anesthesia will have genetic profiling, drug metabolizing enzymes, carrier proteins, and receptors to detect life-threatening risk factors, as part of their preoperative screening. All these will enable anesthetists to provide personalized care using agents that their pharmacokinetic profile are best suited to those individuals. Hence, in our era of evidence-based practice, clinical studies that attempt to evaluate the "OMICS" area would undoubtedly reinforce the body of evidence conducive to tailoring medicine, and would offer targeted drug choice and dosing based on each individual's genetic profile.

Microbiomics

When metadata on human microbiome are considered, the entire microbiota-host-exposome phenotype can be generated for each patient, including microbiome profiling that complement the phenotype of the disease (metadata or phenomics data). Moving from omics' or big data to fused and small data, the stratification of the patients can be tremendously improved, translating this process into a potential better health care and go toward generation of decision-support systems for optimized diagnostic pipelines and clinical interventions (Dabbagh 2020).

Proposed and possible mechanisms of which the intestinal microbiome influences the host response during GI surgeries are as followings: surgical stress, blood loss, starvation, release/suppression of host compensatory signals (cytokines, opioids, ischemic metabolites), shift in community structure, diversity and phenotype (virulence), bacterial information processing, Iterative loop of intra species, interspecies and interkingdom signal exchange) and pathoadaptive immune response (ileus, leak) (Duneau et al. 2011).

The vast majority of wound infections occur as a result of intraoperative microbial contamination. Ileus is due to excessive and inappropriate handling of the bowel during surgery and the inappropriate use of opioids. When a patient is operated on by a high-volume, well trained, and highly experienced surgeon and

develops an anastomotic leak, it is due to a technical error (ischemia, tension, poor technique) (Ljungqvist et al. 2017).

Results of a recently performed study showed that the gut microbial compositions in post-surgery colorectal cancer patients were significantly different from those in pre-surgery colorectal cancer patients and healthy individuals and had a significantly lower alpha diversity and a looser ecological interaction network. This change in in these patients was significantly associated with lymphatic invasion. We can conclude that microbiota was probably considered to be the valuable biomarkers in evaluating the condition of post-surgery colorectal cancer patients and recovering the intestinal health (Drago 2019). Mucus microbiome of anastomosis tissue during surgery has a predictive value for colorectal anastomose leakage. Patients seem to have a higher risk of developing anastomosis leakage when their microbial diversity is low, which in turn is often associated with an overabundance of members from the mucin degrading families Lachnospiraceae and Bacteroidaceae (van Praagh et al. 2019). Using fecal microbiota transplantation can decrease the surgical induced dysbiosis and use as a targeted strategy in personalized anesthesia in perioperative period for decreasing post op complications (Wang et al. 2019). Schmitt et al showed the same results for decreasing postoperative complications after pancreatic surgeries (Schmitt et al. 2019). For making surgery safer and further reduce complications, a molecular, genetic and functional understanding of the response of the gastrointestinal tract to alterations in its microbiota is needed. Methods can then be developed to preserve the health-promoting functions of the microbiota while at the same time suppressing their harmful effects.

Personalized Medicine in Bariatric Surgeries

Bariatric surgery has increased dramatically in the past two decades due to data demonstrating decreased long-term mortality and disease burden and cost-efficacy (Butler and O'Rourke 2013). From a practical view, however, adequate resources in the form of health care dollars and surgeons simply do not exist to offer surgery to all candidates. Patient selection is therefore of critical importance. The results of Zechner et al. study showed that MC4R can be used as a predictor of diabetes remission. So this marker can be used as a screening test for selection of patients who are candidate for bariatric surgery and have concurrent diabetes mellitus (Zechner et al. 2013).

On the other hand, surgical management of obesity requires understanding the genetic and epigenetic factors that play a crucial key role in obesity development and weight loss response. Given the concepts of nutritional genomics, defining a "nutrigenomic risk score" or a "nutrigenomic profile" for each individual may represent a novel therapeutic approach for the management of obese patients submitted to bariatric surgery as a targeted therapy for personalized anesthesia (Nicoletti et al. 2017).

There is strong academic and public interest in advancing personalized medicine, which promises more precise, efficient patient care. The infrastructure of a successful personalized anesthesia should have four essential components (Iravani et al. 2017; Sezari and Dabbagh 2019):

1. Genomic/molecular data acquisition,
2. Integration of genomic diagnostic testing and targeted imaging,
3. Research focused on functional genomic targets, and
4. Development and informed use of targeted therapies/drugs of actionable genes

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Chapter 10
Personalized Critical Care Medicine

Aditi Balakrishna and Abraham Sonny

Defining Our Terms

The term "personalized medicine" first came into use following the completion of the human genome project in 2003, when Dr. Leroy Hood coined the phrase to describe the use of individual genetic signatures to risk stratify individuals and therefore enact targeted preventative strategies for disease (Hood 2003). Since that time, other terms have come about, including P4 medicine (predictive, personalized, preventative, and participatory) (Hood and Friend 2011), precision medicine, and individualized medicine. All of these seek to prompt clinicians and researchers to acknowledge the heterogeneity in people and diseases themselves, and approach treatment accordingly (Agusti et al. 2015).

The terminology surrounding this concept has further nuance and variation that warrants clarification. Ideally, a "personalized" approach should allow for targeted treatments for groups with defined biological features, but how these groups are defined and studied varies in the literature. For instance, instead of "personalized" medicine, some advocate the use of the term "strata" to refer to groups of patients with similar features, thus resulting in the term "stratified" medicine (Hingorani et al. 2013). Others use the term "phenotype" to define populations based on a condition's clinical presentation that can therefore be used as criteria for study enrollment.

When these groups have similar presentations but have subclinical differences, they can be further broken down into "endotypes," a term that implies an understanding of biological mechanism for a presentation (Lotvall et al. 2011). In practice, however, the mechanism may not be known, so these subgroups may be

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referred to as subphenotypes (Bhatraju et al. 2016), but this term, too, has variable connotation, so the term "subtype" is occasionally used (Thompson et al. 2017). The purpose of these groupings is to help guide therapy and improve outcome, but the terms defining outcome also vary. The word "prognostic" implies that a given quality portends or is associated with a specific outcome. The term "predictive" is similar, but the outcome in question is more specifically related to drug or device responsiveness.

How Does Personalized Medicine Influence Critical Care?

The impact of personalized medicine on critical care can be seen in the following five areas: risk stratification, diagnosis, treatment plans and response, prognostication, and research.

Stratifying clinical risk has significant implications for triage and timing of intervention. For example, predicting which of our patients are at highest risk of developing Acute Respiratory Distress Syndrome (ARDS) or Acute Kidney Injury (AKI) may allow us to intervene upon those individuals sooner and in a more informed manner. Tools to make more accurate diagnoses (e.g. does an individual have sterile inflammation or a bacterial infection?) have immense implications for patient outcome and resource utilization. Tailoring treatment plans to those most likely to respond to a given intervention increases the impact of what we do and decreases unnecessary off-site effects; for example, we know that there are different responses to the commonly used sedative dexmedetomidine (Holliday et al. 2014) and variations in adverse events during use of vasopressin (Anantasit et al. 2014). Personalized medicine may help us prognosticate for critically ill patients, which is vital for care planning on a systems and individual level. Finally, Seymour et al. (2017) outlined three ways in which personalized medicine could impact research: (1) retrospective studies can uncover associations that are predictive or prognostic of a given outcome, (2) treatment response characteristics (e.g. determining patient subsets who might benefit from a particular drug) can guide trial enrollment strategies in order to enrich groups (Meurer et al. 2012), and (3) heterogeneity of treatment effect can be identified post-trial by determining which treatment strategy work better in some patients versus others (Iwashyna et al. 2015).

The promise of this approach seems substantial, and many areas of medicine have begun to harness these tools, particularly oncology. But critical care medicine has become increasingly protocol-driven, especially since the positive outcomes associated with early goal-directed therapy were seen in sepsis (Rivers et al. 2001). Indeed, there has been a push toward checklists and bundles to standardize care to a population, while personalized medicine would seek to individual care to a single patient or small group of patients. And while this approach has improved outcomes in many arenas, there are limitations to this strategy, and on a practical level,

patients' clinical course often requires clinicians to practice in an individualized fashion. Currently, this individualization may or may not be based on evidence and may vary greatly between different clinicians. Advances in personalized medicine will allow this to be implemented based on strong evidence and in a much higher-fidelity manner.

What Tools Do We Have to Bring Personalized Medicine to the Intensive Care Unit?

While the current utilization of personalized medicine in the intensive care unit (ICU) may be limited, the tools abound in the research space to improve this going forward. These include biomarkers, the use of large data (neural networks and artificial intelligence), and the various flavors of Omics. Application in specific disease states will be discussed later in the chapter.

A biomarker is a physiologic or molecular characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to therapeutic intervention (Biomarkers Definitions Working 2001). Biomarkers play a role in diagnosis, treatment monitoring, and outcome stratification, and they can serve as surrogate endpoints in clinical research (Sandquist and Wong 2014). They have been studied in numerous critical illness disease states, including ARDS, AKI, sepsis, and pulmonary embolism.

The sheer volume of genetic data that exists for analysis provides untold opportunity to further our understanding of critical illness disease states. In fact, some estimates suggest that since the Human Genome Project was completed, the volume of data has grown tenfold each year (Berger et al. 2013). The term "omics" describes the identification and use of specific genetic markers to improve fidelity of diagnosis and treatment. These markers include genes, single nucleotide polymorphisms (SNPs), proteins (cell signaling molecules, those that influence DNA expression, etc.), messenger RNA, and metabolites. Again, the role of this type of inquiry in furthering our understanding of specific disease states will be discussed later in the chapter, but this approach is also frequently utilized to further our understanding of drug therapy (both response and adverse effects), which is called pharmacogenomics.

As more ICUs begin to use electronic health records, physiologic and lab data is accruing automatically. Processing and analyzing this mass of data may require leveraging neural networks and artificial intelligence systems that can appropriately mine and process this information. While these methods may not provide mechanistic information, they can help provide real-time feedback about data as it is generated such that study models can adapt continuously.

Current Status of Personalized Medicine in Critical Care

Though admission to the intensive care unit occurs due to a variety of disease processes, morbidity and mortality in ICU is largely related to organ system failure. Despite various process improvement strategies geared to improving outcomes in the ICU, mortality still remains high. The leading cause of death in the ICU is from multi-organ failure, which is the final common pathway for various etiologies causing critical illness (Waydhas et al. 1992; Orban et al. 2017). Among critically ill patients, the incidence of mortality is 15–28% when more than one organ system fails (Elias et al. 2015).

The underlying pathophysiological heterogeneity of various clinically similar diagnoses in the ICU calls for personalized medicine to improve outcomes. With current technological advancements we are able to leverage the whole spectrum of data from various omics-based approaches to real time artificial intelligence-based decision making to institute targeted therapy in ICU. Below we describe the current status of various precision medicine approaches to different clinical questions and common scenarios encountered in an ICU.

Pharmacogenomics in the ICU

Pharmacogenomics is actively used in the oncology space, and approximately 10% of all drugs have pharmacogenetic information and/or recommendations included in their product labeling (Hamburg and Collins 2010; Allen and Gelot 2014). Much of the existing work in this space has been in elucidating the SNPs of the cytochrome P-450 (CYP) enzymes, which are central to the metabolism, absorption, distribution, and elimination of many drugs. Applications in the ICU setting remain limited, likely because of the impact of critical illness on basic pharmacokinetic and pharmacodynamic variables—like volume status and organ function—as well as significant polypharmacy in this population. There are, however, a number of medications commonly utilized in the ICU for which there are known SNPs that affect drug function. These include opioids (genetic variations impact pharmacokinetics/pharmacodynamics), clopidogrel (CYP2C19 polymorphisms affect levels of platelet inhibition), coumadin (CYP2C and VKORC1, a vitamin K-related gene) (Bodin et al. 2005), succinylcholine (butyrylcholinesterase) (McGuire et al. 1989) and procainamide (N-acetyltransferase-2) (Hamdy et al. 2003).

Two commonly utilized drugs in the ICU that have been examined in this manner are the sedative dexmedetomidine and vasopressin. Dexmedetomidine is an alpha-2 agonist commonly used for sedation, but it can also be associated with hypo- and hypertension depending on the dose and speed of administration. Clinically, however, there is a wide variability in susceptibility to sedative effects as well as in blood pressure response. Holliday et al. (2014) examined the existing studies looking at the effect of alpha-2 adrenoreceptor polymorphisms, CYP2A6 (encodes the

enzyme responsible for metabolism of dexmedetomidine), and the uridine diphosphate gluconosyltransferase genes responsible for non-CYP metabolism, on sedation and blood pressure effects. Only one study demonstrated a positive result, which demonstrated that a specific allele of the ADRA2A alpha-2 adrenoreceptor gene reduced efficacy and increased time to effect after receiving dexmedetomidine, however, the result has not yet been replicated (Esteller 2008).

Vasopressin has also been studied, where SNPs in genes related to its action site were investigated. Although the result has not been replicated, the authors found that serious adverse events were associated with a presence of an SNP near AVPR1a, a vasopressin receptor gene (Anantasit et al. 2014).

Can We Predict Individuals Who Are More Susceptible to ARDS or Are at Higher Risk of Adverse Outcomes?

Risk factors associated with ARDS development and its severity has been studied using various omics approaches including candidate gene association studies, genome wide association studies, and whole-exome sequencing (Reilly et al. 2017).

Candidate gene association studies investigate the association of ARDS risk with a set of a priori selected genes, which are known to be linked to biological mechanism of ARDS. These studies have identified several genes associated with ARDS susceptibility and outcome. Some notable examples are, a functional variant in the gene encoding for angiotensin converting enzyme, ACE I/D polymorphism genotype, has been associated with a higher mortality risk (Matsuda et al. 2012). An SNP in the advanced glycosylation end-product specific receptor (AGER) gene (encoding a marker of pulmonary epithelial injury) confers a higher risk for developing ARDS as well as a higher mortality among patients with ARDS. Susceptible patients also have a higher plasma concentration of sRAGE (soluble receptor advanced glycosylation end-product), a measurable biomarker (Jabaudon et al. 2018). Two functional polymorphisms of IL17 has been associated with significant risk and prognosis in ARDS (Xie et al. 2019). On the other hand, some candidate genes have been found to be protective. A genetic variant of the leucine-rich repeat-containing 16A (LRRC16A) gene, which has a role in platelet formation, reduces ARDS risk (Wei et al. 2015). Studies have revealed at least 90 candidate genes associated with ARDS, but its relevance has been questioned due to lack of reproducibility and difficulties in interpretation (Hernandez-Beeftink et al. 2019).

Only two genome wide association studies (GWAS) have evaluated ARDS susceptibility, one evaluating trauma related ARDS and the other evaluating all-cause ARDS (Christie et al. 2012; Bime et al. 2018). Although no locus achieved genome wide significance, marginal significance was seen in more than 150 loci. Both studies were able to reveal previously unknown ARDS susceptibility genes. Other investigators have used Mendelian randomization analysis, which explores the genetic variability in intermediate features of ARDS, which might have a causal

relationship with ARDS. In addition to risk stratification, identification of such causal relationships may also help develop individual specific therapeutic targets. For instance, Mendelian randomization analysis showed that plasma levels of plasma angiopoietin-2, a biomarker of endothelial permeability and activation, was strongly associated with ARDS (Wada et al. 2013). Additionally, genetic variation in the angiopoietin-2 gene (ANGPT2) has been linked to risk of ARDS (Su et al. 2009). Pharmacological modification of angiopoietin-2 levels or its signaling may bring us close to using precision medicine for prevention or treatment of ARDS (Reilly et al. 2018).

In addition to omics methods, clinical prediction scores exist for quantifying ARDS risk. The most widely studied among them is the Lung Injury Prediction Score, which was derived from a cohort of more than 5000 patients who were at risk of acute lung injury at hospital admission, and among whom 7% developed acute lung injury (Gajic et al. 2011). The input to the score consists of a variety of variables including co-morbidities and presenting diagnosis. Prediction scores can be used with biomarkers to improve predictive ability. After studying various plasma biomarkers of ARDS, Xu and colleagues concluded that angiopoietin-2 plasma levels markedly enhanced the ability of Lung Injury Prediction Score to predict ARDS (Xu et al. 2018).

Can Ventilation Strategies Be Individualized to Patients?

Though key advances in lung protective ventilation and resuscitation has improved mortality from ARDS, the morbidity and mortality associated with ARDS remains substantial (Phua et al. 2009). The landmark ARDS net trial demonstrated that ventilating patients with a low tidal volume (4–6 ml/kg of predicted body weight) improved mortality, when compared to a higher tidal volume strategy (Acute Respiratory Distress Syndrome Network et al. 2000). No subsequent ventilation strategies have consistently reduced mortality in ARDS.

Mechanical ventilation could worsen lung injury in ARDS as well as among patients with normal lungs. A heterogenous portion of the lung remains collapsed or atelectatic in ARDS, and contributes to secondary inflammation and lung injury. Presence of atelectasis during mechanical ventilation causes lung injury in at least two ways, (1) dynamic recruitment and de-recruitment with each breath causing dynamic strain, and (2) stress concentration which occurs between open and collapsed alveoli (Nieman et al. 2017). It is well known that application of positive end expiratory pressure (PEEP) reduces atelectasis, improves lung compliance and potentially reduce lung injury, however, the amount of PEEP which is most beneficial is unclear. Various studies have evaluated a low versus high PEEP strategy and has found neither to be superior (Briel et al. 2010). However, the emerging concept is that rather than one strategy fits all, the amount of PEEP applied needs to be personalized based on patient characteristics and type of lung injury.

Various strategies are currently being explored to personalize PEEP. Traditionally, optimal PEEP has been decided by what leads to best oxygenation, or best compliance. Setting PEEP based on lung compliance (i.e., setting PEEP which results in the highest compliance) logically makes sense, especially since compliance is predictive of mortality (Amato et al. 2015). Another strategy is to choose the minimum PEEP needed to keep open all recruitable portions of the lung, and hence minimize atelectasis. This can be achieved by various methods. Volumetric capnography allows calculation of dead space, and hence allows personalizing PEEP in each patient to minimize atelectasis (Suarez-Sipmann et al. 2014). This is valuable, since increased dead space is independently associated with mortality in ARDS (Cepkova et al. 2007). More recently, investigators have used bedside imaging modalities like lung ultrasound to monitor atelectasis and thereby titrate PEEP. A novel bedside device, electrical impedance tomography, has become available which allows measurement of regional variations in lung ventilation at bedside (Bikker et al. 2010). Animal studies have shown that electrical impedance tomography guided ventilation improved regional and global lung compliance and reduced lung injury as shown in histopathology (Wolf et al. 2013). Another approach to minimize atelectasis is to maintain PEEP marginally above the transpulmonary pressure (airway opening pressure minus pleural pressure) (Talmor et al. 2008). Pleural pressure is estimated via esophageal manometry. Although various strategies are available to personalize PEEP, the best strategy remains unknown, and needs further evaluation.

Is There Evidence for Different Endotypes in ARDS and Can Treatment Be Personalized Based on These Endotypes?

Very few strategies, other than low tidal volume ventilation, has shown to improve outcome in patients with ARDS. A likely explanation is that most ARDS trials have applied strategies to the whole ARDS cohort, and it is possible that some of these strategies might be better effective in certain subset of ARDS patients. This is supported by the fact that ARDS is a heterogenous disease and tailoring therapy to endotypes may facilitate therapeutic discovery.

Calfee et al. has used latent class analysis to identify subgroups among patients with ARDS. Latent class analysis uses mixture modelling to identify the best fitting model based on a set of variables, assuming that the sample contains various unknown groups. It explores presence of subgroups within a cohort defined by a similar combination of baseline variables. Using clinical and biological variables available from previously published ARDS studies, Calfee et al. (2014) identified two subgoups: a hyperinflammatory phenotype characterized by higher levels of inflammatory biomarkers, shock, metabolic acidosis, and mortality, and a second, non-hyperinflammatory phenotype. These clinical phenotypes were also found to be stable over a period of time (Delucchi et al. 2018).

As expected, these two phenotypes respond differently to therapeutic strategies. In a cohort of 1000 patients with ARDS, Famous et al. (2017) found that a restrictive fluid management strategy reduced mortality in the hyperinflammatory group, while increased mortality in the non-hyperinflammatory group. Similarly, statins improved survival in the hyperinflammatory phenotype (Calfee et al. 2018). To facilitate easier identification in a clinical setting, Famous et al. (2017) found that measuring serum concentrations of interleukin-8, bicarbonate, and tumor necrosis factor receptor-1 can be used to identify the hyperinflammatory sub-phenotype with excellent accuracy.

Can We Predict Susceptibility and Survival of Sepsis?

Sepsis is a heterogenous disease which is influenced by various factors including immune status, genetic predisposition, pathogen type, and extend of infection. Genetic variation may influence the risk of disease and its clinical evolution. Such variations have been studied in an attempt to develop novel personalized therapeutic strategies. Candidate gene association studies of sepsis susceptibility and outcome has looked at a variety of target genes. For instance, certain toll like receptor-1 polymorphisms have been associated with organ dysfunction, proinflammatory responses and sepsis outcome (Wurfel et al. 2008; Pino-Yanes et al. 2010; Thompson et al. 2014). However, the results of these studies have often been inconsistent and not reproducible in different populations, potentially because the populations studied have been small and heterogenous (Clark and Baudouin 2006).

GWAS could circumvent some of these limitation by performing a relatively unbiased evaluation of genomic risk. Until now, three genome wide association studies have been published in sepsis (Man et al. 2013; Rautanen et al. 2015; Scherag et al. 2016). Rautanen and colleagues used GWAS to explore association of 6 million SNPs with 28-day mortality after sepsis from community acquired pneumonia. Among the 11 loci identified, an SNP in the intronic region of FER gene within chromosome 5 was consistently associated with mortality in all examined cohorts (Rautanen et al. 2015). Scherag and colleagues also evaluated 28-day mortality in adult patients with sepsis. They found 14 loci, none of which overlapped with the loci found by Rautanen, or with FER gene (Scherag et al. 2016). This lack of reproducibility reduces clinical utility, however, studying more homogeneous populations and larger sample sizes may provide clinically useful associations.

Another promising approach to predict development of sepsis, is by using high-resolution vital signs data and electronic medical record data. This has been used to develop clinician decision support tools which can identify patients at highest risk of future sepsis (Nemati et al. 2018). Development of these tools harness complex artificial intelligence based machine learning techniques including deep learning using long short-term memory neural networks (Saqib et al. 2018). A recent meta-analysis found that machine learning models outperform traditional sepsis scoring system such as sequential organ failure assessment score (Islam et al. 2019).

What Is the Role of Metagenomics in Sepsis?

Metagenomics is the study of genetic material recovered directly from an environment. It has been used to study the microbiome, i.e., the genetic material of all microbes living inside or on the human body. Intestinal microbiome forms a complex ecosystem and is involved in a wide array of functions including production of hormones and host immunity. Changes in diversity and quantity of gut microbiota, called dysbiosis, alters host immunity to pathogens and may increase susceptibility to infections and sepsis. In addition to intestinal microbiome, the respiratory microbiome is also markedly altered in patients with sepsis (Lee and Banerjee 2020). Better understanding of the relationship between human microbiome and host immunity will help develop strategies to favorably modulate microbiota, and develop a personalized therapy for individuals with dysbiosis.

Modulation of gut microbiota can be achieved by administration of a pool of microbes normally found in gut (probiotics), and/or by improving the intestinal microenvironment using agents which favor growth of normal gut microbiota (prebiotics) (Haak et al. 2018). A meta-analysis of 30 studies evaluating the effect of probiotics in critically ill patients showed significant reduction in infections including ventilator associated pneumonia, but no effect of mortality or length of stay (Manzanares et al. 2016). A randomized controlled trial of 4500 infants in rural India found that administering a combination of *Lactobacillus plantarum* (probiotic) and fructooligosaccharide (prebiotic) reduced mortality and incidence of sepsis (Panigrahi et al. 2017). Fecal microbiota transplantation is another strategy to treat dysbiosis, and is now commonly used to treat recurrent *Clostridium difficile* infection. Regulating human microbiota in individuals with dysbiosis is an emerging area of research, and may have potential to reduce the incidence of sepsis, improve immediate outcomes and reduce long term mortality after sepsis.

Can We Differentiate Sepsis from Non-infectious Inflammation?

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. Hence, a diagnosis of sepsis has two components, presence of organ dysfunction and suspicion or presence of infection. The presence of organ dysfunction is easily quantified based on the numeric sequential organ failure assessment score. However, tools for differentiating infection from non-infectious inflammation are limited, and is largely based on clinical suspicion. Current gold standard for identification of infection is microbial growth of a pathogen in culture media. However, culture based techniques suffer from various limitations including long time to diagnosis, and poor sensitivity. Each hour delay in administration of effective antimicrobial therapy is associated with a measurable increase in mortality in various studies. This has led to inadvertent antimicrobial therapy causing inadvertent toxicity, increased cost, and growth of antimicrobial resistance.

Development of a biomarker to diagnose sepsis with precision will help target delivery of antimicrobial agents to only individuals with infection. Over 150 protein and cytokine biomarkers has been studied in the context of sepsis. Procalcitonin is by far the most commonly studied, has been shown to be specific for bacterial infection in various patient populations. A recent meta-analysis shows a pooled sensitivity of 0.77 and pooled specificity of 0.79 for procalcitonin to differentiate infection from non-infectious inflammation (Wacker et al. 2013). Other biomarkers such as C-reactive protein and interleukin-6 are equally elevated in both infection and non-infectious inflammation, limiting their utility.

Recently, there has been interest in utilizing systems biology based approaches to identify differences in host transcription response between infection and non-infectious inflammation (van Engelen et al. 2018). Use of RNA molecules as biomarkers has the advantage of them being incorporated into polymerase chain reaction based bedside testing, making them attractive for integration into rapid clinical decision making. Three diagnostic RNA marker panels which have been studied in this context, specifically, sepsis meta score (Sweeney et al. 2015), septicyte lab (McHugh et al. 2015) and FAIM3:PLAC8 (Scicluna et al. 2015), with promising results. Sepsis meta score and septicyte lab consists of a panel of 11 and 4 gene transcription products respectively, and has been developed to diagnose sepsis. While FAIM3:PLAC8 gene expression ratio was developed to diagnose community acquired pneumonia. These tools await further trials before they can be incorporated into sepsis diagnostic algorithms.

Can We Personalize Antibiotic Regimens in Sepsis?

Choosing an effective antibiotic regimen as well as administering it early in the course of disease markedly improves sepsis survival (Rhodes et al. 2017). Culture based methods remains the gold standard and are most widely used to identify the type of microbial infection (viral versus bacterial) and presence of antimicrobial resistance. However, these take days to report and have a high rate of false negative results.

Identifying the pathogen early on will favor a more effective and personalized approach to choosing antimicrobial agents. Bacterial and viral infections lead to different host immune responses. Based on the concept that bacterial and viral agents generate different responses in the host, Tsalik and colleagues identified transcriptomic biomarkers to differentiate between bacterial and viral agents causing an acute respiratory illness (Tsalik et al. 2016). This was validated in publicly available genomic databases showing high sensitivity and specificity (AUC > 0.9). Several rapid molecular pathogen specific diagnostic tools have been developed for early identification of the causative microbial agent. Pathogen specific assays are not sufficient by themselves due to large number of pathogens which can cause sepsis. However, they can be used to rule out (or confirm) certain infections like malaria and dengue. Various multiplex polymerase chain reaction based tests are available which can detect a predetermined array of bacteria and fungi. Some of them allow for

detection of certain resistance genes as well. For instance, *Staphylococcus aureus* acquires methicillin resistance by insertion of mecA gene into its chromosome, which can be detected by polymerase chain reaction based techniques (Wang et al. 2013). It is also being used to identify certain genotypes of vancomycin resistant enterococcus, specifically VanA, and VanB (Seo et al. 2011). Majority of these tests provide no information on antimicrobial susceptibility. These tests can be used directly on clinical specimens or after its enrichment in a culture medium. However, direct detection has many disadvantages including false positive rate, contamination, and interference with human DNA. Hence, rapid molecular diagnostic tests has some role in early detection and pathogen identification in sepsis, but in their current status they complement rather than replace microbial culture data (Rello et al. 2018).

Is There Evidence for Endotypes in Sepsis and Instituting Endotype Specific Treatment Strategies?

Various investigators have used transcriptomics to identify various sepsis endotypes, which might have therapeutic and prognostic implications. Wong and colleagues identified two subgroups (A and B) among pediatric septic shock patients, based on a 100-gene expression panel representing adaptive immunity and glucocorticoid receptor signaling pathways. Subgroup A, where these genes are down regulated, has worse clinical outcomes (Wong et al. 2015). Using predictive enrichment strategies, they were able to show that subgroup B is more likely to benefit from corticosteroids (Wong et al. 2016). This could pave way to conducting future trials evaluating effect of corticosteroids in sepsis, in an enriched cohort.

Similarly, Davenport and colleagues used a similar approach to identified two transcriptomic signatures, sepsis response signature 1 and 2, among critically ill patients with community acquired pneumonia. Surprisingly, there was no difference in expression of proinflammatory cytokine genes between the two groups. Sepsis response signature 1 was associated was a much higher mortality (Davenport et al. 2016). Sepsis endotypes represented by sepsis response signature 1 and 2 has also been replicated patients who developed sepsis from peritonitis (Burnham et al. 2017). Predictive enrichment based on these endotypes may be useful in developing treatment strategies which work on a specific subgroup.

Can Fluid Management Be Personalized Among Patients with Septic Shock?

The surviving sepsis guidelines suggest initial resuscitation with 30 ml/kg of crystalloids within 3 hours of presentation (Rhodes et al. 2017). In the past, guidelines advocated for early goal directed fluid therapy based on trial by Rivers et al. in 2003 (Rivers et al. 2001). Subsequently, three randomized trials showed no improvement in outcomes with early goal directed fluid therapy (ARISE Investigators et al. 2014;

Pro et al. 2014; Mouncey et al. 2015). In fact, a meta-analysis of these three trials showed that broad protocolized approaches like early goal directed therapy leads to larger fluid administration, a higher ICU admission rate and increased ICU resource utilization (Angus et al. 2015). Subsequently, the latest surviving sepsis guidelines from 2016 recommend a more personalized approach to fluid therapy. They recommend that fluid resuscitation (after the initial bolus) be based on dynamic indices of volume responsiveness, measured in each patient (Rhodes et al. 2017). These include stroke volume variation and pulse pressure variation, but such indices are not reliable in patients who breath spontaneously or has arrhythmias. Further clinical trials are needed to identify optimal strategy to personalize fluid therapy in septic or distributive shock.

Can We Predict Who Will Develop Acute Kidney Injury?

AKI refers to a spectrum of renal dysfunction, ranging from minor dysfunction to the need for replacement therapy. AKI is immensely important and common in the critical care setting. Variability in definition of AKI has rendered exact incidence difficult to determine, but it has been reported as being between 22% and two thirds of all ICU patients (Hoste and Kellum 2006), and numerous studies have demonstrated an association between AKI and adverse outcomes including mortality.

At present, our ability to predict the development, severity and impact of AKI on each patient is limited. Serum creatinine and urine output are the most commonly used metrics for assessing renal function. The limitation of creatinine, however, is that it is a surrogate for glomerular function and does not provide information about tubular function; its rise may also lag days behind actual insult, so intervention may begin after significant tubular damage (Koyner and Parikh 2013). Given these limitations, biomarkers that can detect injury early on can help institute treatment strategies personalized to that individual.

Neutrophil gelatinase-associated lipocalin (NGAL)—also known as siderocalin or lipocalin-2—is a molecule that scavenges pericellular labile iron released from organelles after an ischemic or toxic insult, which may help attenuate oxidative stress during injury. It is expressed in multiple types of epithelia throughout the body, including renal tubular cells, and appears to be substantially upregulated in AKI. It has been shown to detect subclinical AKI both prior to a rise in creatinine and without a rise in creatinine (Haase et al. 2011). NGAL is available for use in routine care in many institutions, allowing for earlier identification of injury. Other molecular biomarkers include enzymes, proinflammatory mediators, structural proteins that are released during tubular damage, markers of glomerular filtration that are reabsorbed by functional tubular epithelium, hormonal markers, and proteins involved in cell cycle regulation (Malhotra and Siew 2017). While studies have identified scores of potential target molecules, which has in turn furthered our understanding of the pathophysiology of kidney injury, their use has not yet impacted clinical outcomes.

Another approach is to identify tests that can give clinicians information about functional organ reserve, similar to stress testing in cardiology (Ronco and Chawla 2016). Ronco's group proposed the use of fixed protein loads for investigating a kidney's ability to increase glomerular filtration rate when faced with stress (Sharma et al. 2016). In addition, Chawla et al. developed a "furosemide stress test," that when used in patients with early AKI was able to identify progression to AKI Network Stage III injury with an area under the curve of 0.87 (Chawla et al. 2013).

Two research groups have recently harnessed machine learning using electronic health record data to develop models to predict the development of AKI using data points that are standardly collected during the course of care. From a discovery cohort of 70,000 inpatients, Koyner et al. developed an algorithm for predicting kidney injury. Their model had a sensitivity of 84% and a specificity of 85% for stage 2 AKI and was able to predict it at a median of 41 h prior to patients meeting diagnostic criteria (Koyner et al. 2018). Tomasnev et al. utilized a deep learning approach to analyze over 700,000 adult patients across 172 inpatient and 1062 outpatient sites to create a predictive model for AKI. They were able to predict 55.8% of all inpatient episodes of AKI and 90.2% of those injuries that would require renal replacement therapy with up to 48 h of lead time over clinical manifestation of AKI. They were also able to generate relevant clinical features to support alerts and provide prediction for lab test trajectory (Tomasev et al. 2019).

Can We Predict Who Will Develop Delirium?

ICU delirium is challenging for patients and caregivers alike, and it has been linked to prolonged admission (McCusker et al. 2003; Aitken et al. 2017), higher rates of readmission (Bokeriia et al. 2009), lower quality of life, increased mortality (Aitken et al. 2017), and worse long-term cognitive function (Marcantonio et al. 2000). Estimates of incidence range from 10 to 90% depending on the factors leading to admission (Maldonado 2008; Devlin et al. 2018). This range may be partially explained by the fact that many patients experience hypoactive symptoms and therefore may not be identified.

The CAM-ICU (Confusion Assessment Method for the Intensive Care Unit) is the most ubiquitous tool to diagnose delirium in current clinical practice; it has been well-validated in large studies, and carries a sensitivity and specificity of approaching 100% (Ely et al. 2001). Early identification of patients at risk for delirium will help direct delirium prevention strategies to patients who might benefit from it. Several delirium prediction tools, including the PRE-DELIRIC (PREdiction of DELIRium in ICu patients) and Lanzhou models has been studied in large cohorts, with AUCs of 0.78 and 0.77, respectively, for predicting delirium (Green et al. 2019). PRE-DELIRIC calculates risk based on age, APACHE-II score, coma status, surgical/medical/trauma/neurology/neurosurgical admission type, infection, metabolic acidosis, degree of opioid consumption, sedative use, serum urea, and presence of urgent admission (Linkaite et al. 2018). The Lanzhou model incorporates

age, APACHE-II score, coma, emergency operation, mechanical ventilation, multiple trauma, metabolic acidosis, history of hypertension, delirium and dementia, and use of dexmedetomidine (Chen et al. 2017).

However, these tools do not provide significant mechanistic insight into delirium. Various investigators have studied biomarkers in delirium to help guide risk assessment, diagnosis, monitoring, and treatment. An exhaustive review by Toft et al. lists twenty biomarkers that are associated with or can detect delirium. These include IL-6, cortisol, prolactin, amyloid, neopterin, metalloproteinase-9 (MMP-9), neutrophil-lymphocyte ratio (NLR), phenylalanine-tyrosine ratio, thioredoxin, serpin family A member 3 (SERPINA3), and 8-iso-prostaglandin F2-alpha, many others. Despite these associations, they concluded that they are not useful in in current clinical practice. However, they propose that the commonly utilized inflammatory and metabolism biomarkers could be evaluated especially for screening and diagnosis of hypoactive delirium, which can be more difficult to diagnose (Toft et al. 2019).

Next Steps for Research

As we identify biomarkers and gene targets involved in critical illness, we will next need to determine which markers are clinically useful—both alone and in combination with other markers—to help with risk stratification, aid in diagnosis, and inform prognostication. Once that is known, high-quality tests that result rapidly and can therefore be used in a clinical setting will need to be developed.

This work requires obtaining, manipulating, and interpreting vast amounts of information on a scale and pace that traditional methods of inquiry and experimentation may not be equipped to handle. Accordingly, study and trial design may well need to innovate in both approach and structure to make this science happen. This era of research will necessarily be multidisciplinary and will require significant collaboration across the preclinical, clinical, and implementation science realms.

In the preclinical space, large cohort studies will be required to find targets for further investigation and testing; this will necessitate large patient samples as well as substantial processing power. Innovation in the clinical trial space may need to be more substantial. Trials in a critically ill population are difficult at baseline, as the population is rarely homogenous and tends to have many comorbid conditions, making individual interventions difficult to isolate or randomize. Traditionally structured clinical trials are addressing this challenge by recruiting enriched trial populations, which will ideally compensate for decreased statistical power with increased treatment effect size. One such study that used this approach was the MON-ARCS trial, which examined the TNF-alpha monoclonal antibody fragment afelimomab in septic shock patients. They specifically targeted patients with high baseline IL-6 levels, who they postulated would have the most effect from this intervention. They were able to show an outcome difference within this patient

subset, although the effect size was not significant in the overall study population (Panacek et al. 2004).

We will discuss two novel trial designs that may help address some of these issues: adaptive platform trials and registry-based randomized controlled trials. Adaptive platform trials involve study protocols that allow for the simultaneous evaluation of multiple treatments within a study population; they harness Bayesian analysis in order to preferentially "randomize" patients to treatments with higher likelihood of effect, thus automatically enriching the treatment group. The "platform" denotes the structural framework that allows this type of study; the platform includes one control arm that allows simultaneous comparison of all other treatment arms. These trials also allow progression between traditional phases of trials based on preset rules within the study design, meaning that there does not need to be arbitrary stretches of time between phase 2 and phase 3 study of a given target (Berry et al. 2015). The I-SPY2 trial is a prime example of this type of study design that has allowed for the rapid identification and approval of a targeted biologic agent for breast cancer treatment. Since its inception in 2010, the trial has investigated twelve therapies in eight biomarker-defined subtypes, and it was able to send neratanib (a tyrosine kinase inhibitor) to phase 3 evaluation with less than 200 patients enrolled due to the adaptive trial design (Park et al. 2016).

Another subgroup of platform trials that utilizes electronic health records to evaluate existing therapies is known REMAP (randomized, embedded, multifactorial, adaptive, platform) studies (Angus 2015). These studies leverage electronic health records to screen for patients who may be eligible and then randomize patients to potential therapies; these studies can also harness adaptive trial design and therefore enrich study populations based on what the trial learns. This strategy is currently being used to investigate treatment approaches for severe pneumonia (REMAP CAP), with funding support from the European Union Platform for European Preparedness Against Re-emerging Epidemics (PREPARE network) as well as the governments of Australia and New Zealand. These collaborative networks are also investigating antibiotics, ventilator strategies, and immunomodulation across over 100 ICUs in Europe (Seymour et al. 2017).

Another approach that harnesses existing data is the registry-based randomized controlled trials, which analyzes data collected for other purposes to answer novel questions (Lauer and D'Agostino 2013). In many parts of the world, large scale data is routinely collected. For instance, nearly all of the 90 hospitals with ICUs in the Netherlands send data to a central database known as the Dutch National Intensive Care Evaluation (NICE) registry; consequently, patient-level information on over half a million ICU admissions can be accessed and analyzed (van de Klundert et al. 2015). Similarly, Australia and New Zealand's Intensive Care Society Adult Patient Database similarly collects data from over two million admissions across 90% of the ICUs from both countries (Stow et al. 2006). These efforts exist in nearly twenty countries at present, and the International Forum for Acute Care Trialists (InFACT) reflects the possibility of collaborative registries in the future (InFACT Global H1N1 Collaboration 2010). From this large-scale data, electronic surveillance systems (also known as ESSs or "sniffers") can be implemented to identify appropriate

patients for trials in real time. This has been actualized in the form of the METRIC Data Mart at the Mayo Clinic, which is a system that automatically receives electronic health records data and has been used to screen patients with AKI (Kashani and Herasevich 2013) and sepsis (Herasevich et al. 2011) and notify trial personnel to approach them for study enrollment in real time.

These processes are ambitious, and to be effective in the clinical space, implementation science must keep pace as well. Perhaps by leveraging existing information frameworks (such as electronic health records), systems that can identify appropriate patients, prompt clinicians to consider targeted therapies, and measure relevant markers of progress and outcome in real time will need to develop and then become part of routine clinical practice (Seymour et al. 2017).

Challenges for Implementation

The future is bright for precision medicine in critical care, but the implementation challenges are real and must be thoroughly understood so that they can be addressed appropriately. First and foremost, translating the findings from basic science research into usable tools that can be implemented with fidelity in critically ill patients with a host of comorbidities is a challenge at present and is likely to continue to pose difficulties. Once these tools exist, they also need to produce usable results on a short time frame that makes sense in an ICU environment. While the technology associated with sequencing and biomarker identification will get cheaper over time, the development of new diagnostic tests and therapeutics—which may need to be marketed to smaller subsets of patients—could confer additional financial burden.

These efforts require collaborative efforts across the globe to standardize measurements and reporting so that when data is shared, we can do so meaningfully (Dzau and Ginsburg 2016). Data storage and security policies will also be necessary to manage this information, in addition to the costs associated with storing, securing, and processing data. As discussed earlier in the chapter, analysis will likely require leveraging artificial intelligence and neural networks, given that we can ask increasingly complex questions, and the computational power required to mine this information will be immense. Furthermore, should we begin to harness the information being generated in ICUs with computerized monitoring and record systems, these requirements will only grow. Electronic health records data, however, does pose additional challenges. Currently, regulatory barriers to utilizing what is generated and recorded in the medical record are high, and the quality of information can be variable, as much of it still relies on human input. In addition, the various electronic health records nation and world-wide do not have standardized ways of representing, storing, or searching for information (Maslove et al. 2016).

What Does the ICU of the Future Look Like?

Personalized medicine in a critical care setting is rife with challenges, but a more targeted approach to ICU patients is certainly possible, and it is likely what is best for many of our patients. We envision a world in which well-developed biomarker tools can be utilized upon patient presentation to aid in diagnosis, risk stratification, and initiation of appropriate care. Upon determining the clinical entity that a patient is facing, targeted tools to monitor response to therapy as well as their organ function (e.g. kidneys, cognitive system) can allow clinicians to adjust course where needed. Decision support tools will be integrated into electronic health records to help clinicians keep up-to-date with the latest data and recommendations. These individualized interventions will likely work hand in hand with checklists and care bundles, which will have their role in ensuring that overall quality of care remains at a high standard. All the while, robust data systems will be seamlessly integrated into clinical care, such that researchers in collaborative groups are able to learn in real time from every patient we see, so that we can continuously iterate the care we provide.

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Chapter 11
Personalized Anesthesia in Hematology

Akbar Dorgalaleh, Mehran Bahraini, and Sayed Esmaeil Ahmadi

Introduction

In spite of 99.5% within the species-homology in the human genome, humans have their unique response to diseases and stimulators such as drugs. Hematological disorders are not excluded from responses to stimulators (Pati and Sharma 2017). Emergence of new genome sequencing technologies, such as next-generation sequencing (NGS) or high-throughput sequencing, is enabling us to tailor a person's treatment to his or her unique gene profile (Gil et al. 2018). Anesthesia is a highly sensitive procedure which closely correlates with hematological conditions that emphasize the need for close and timely collaboration between hematologist and anesthetist/anesthesiologist. Both general and regional anesthesia can affect a person's respiratory, hemostatic, hemodynamic and endocrine systems (Brueckner et al. 2003; Torpy et al. 2011; Sano et al. 2016; Smith and Goldman 2018). Anesthesia methods have varied effects on a patient's physiological systems. By combining conventional and precision medicine, cutting-edge technologies can provide better patient management (Badalian-Very 2014; Collins and Varmus 2015). Anesthesia has potential effects on hematological parameters, including a patient's blood profile and coagulation indices. Hence, clinical and familial history, medication and patient characteristics, along with preoperative blood tests such as complete blood count (CBC), prothrombin time (PT)/international normalized ratio (INR) and activated partial prothrombin time (APTT), should be considered (Akhunzada et al. 2018; Alzahrani et al. 2019). Anesthesia drugs differ in their metabolism and efficacy, based on the genetic profile of each person, which indicates the importance of pharmacogenetic/pharmacogenomic. Pharmacogenomic, the cornerstone of personalized

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medicine, can make clearer the physician's comprehension of individual response to treatment based on one's genome profile (Behrooz 2015; Gabriel et al. 2017).

Hematological Considerations for Anesthesia

CBC, blood film evaluation and coagulation tests are common preoperative laboratory assays. These tests can help in the diagnosis of immunodeficiencies, infection, anemia, polycythemia, some malignancies, and hemorrhage. Along with clinical features, they can facilitate choosing the appropriate type of anesthesia and surgery (George-Gay and Parker 2003; Kumar and Srivastava 2011). As each patient has a unique gene profile, one might exhibit a significant feature such as a congenital or acquired abnormality. Therefore, each patient should be prepared and treated according to their genetic profile, along with the results of basic and specific tests (Vogenberg et al. 2010).

Anesthetic Considerations in Erythroid Disorders

Anemia

From the point of view of anemia, genome sequencing can help us determine which medical care would be most useful for patients, because some gene variations determine how a patient responds to a drug or procedure. These data can be provided by micro-array and whole-genome sequencing technologies such as NGS and Sanger sequencing. The patient's lifestyle, environment, socio-economic status, diet, age, and sex also should be considered for better treatment (Iolascon et al. 2015). For example, treatment of chronic hepatitis virus (HCV) infection with ribavirin (RBV) has the potential to induce acute hemolytic anemia (AHA). It has been demonstrated that inosine triphosphatase (ITP) deficiency is an overriding protective factor against RBV-induced AHA. Knowledge of patients' genetic variations can improve their medical care or enable us to anticipate some complications (Fellay et al. 2010; Clark et al. 2013; Iolascon et al. 2015). In personalized medicine, the detection of anemia can be started by an individual by him/herself anytime, anywhere, instantaneously and remotely, with the help of new smartphones and specific applications (Mannino et al. 2018). Preoperative anemia is a great threat to a patient. Published protocols have recommended that red blood cell (RBC) indices such as hemoglobin and hematocrit should be checked at least 1 month before surgery to provide proper intervention (Burton et al. 2018). Erythrocyte sedimentation rate (ESR) usually is performed before, and occasionally after, surgery. However, several studies have shown that anesthesia has no bearing on an increase in ESR (Caglayan et al. 2006; Mirzayan et al. 2009; Bilehjani et al. 2017). Furthermore, not only is anemia a challenge to anesthesia, sometimes anesthesia can cause anemia. In both situations, considering

patient status, specific measures should be taken to avoid further complications. In the matter of erythrocyte recovery after surgery, a study that compared the effects of three anesthetic techniques—epidural anesthesia, general anesthesia, and the combination of both techniques—on RBC endogenous recovery showed that epidural anesthesia administration had a notably higher recovery rate of the circulating erythrocyte mass than those who received general anesthesia or the combination.

Non-immune Hemolytic Anemia

Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency

The most prevalent enzyme deficiency in the world is glucose-6-phosphate dehydrogenase (G6PD) deficiency, an X-linked non-immune hemolytic anemia that can become an impediment to anesthesia and surgery. It affects more than 400 million people worldwide, most commonly of African, Mediterranean, and Asian descent (Dorgalaleh et al. 2013b; Richardson and O'Malley 2018). G6PD protects cells, especially RBCs, against oxidative damage from the ingestion of fava beans, infections, metabolic conditions like diabetic ketoacidosis, and certain anesthetic drugs such as benzocaine, lidocaine, prilocaine, and articaine. Importantly, in the anesthetic management of G6PD patients to avoid hemolysis, any oxidative agent, such as 8-aminoquinolines for treating malaria, sulphur-containing antibiotics, rasburicase, high doses of aspirin, and paracetamol should be limited as all can cause hemolysis (Elyassi and Rowshan 2009; Valiaveedan et al. 2011; Luzzatto and Seneca 2014; Hwang et al. 2018). Nitrate is part of anesthetist's armamentarium; though hemolysis by nitrate can be induced without G6PD deficiency, G6PD deficient patients are more vulnerable to it (Wong et al. 2013). Additionally, a very recent study found that administration of sevoflurane, a common anesthesia drug, can lead to a temporary increase in the antioxidant defense system of cells (Zhou et al. 2018). To date, more than 190 genetic variations of G6PD have been found that can change the course of a patient's treatment due to vulnerability to assorted drugs and agents. It has been suggested that G6PD be classified as a candidate in the matter of pharmacogenomic in its hotspot zones, which might lead to specific treatment (Fig. 11.1) (Manjurano et al. 2015; Goh 2018).

Furthermore, a new quantitative point-of-care test, called The SD Biosensor STANDARD G6PD test, provides sensitivity and specificity of 100% and 97%, respectively. Potentially, this test can improve health outcomes (Pal et al. 2019).

Hereditary Spherocytosis

In cases of non-immune hemolytic anemia, especially in cases with liver dysfunction, jaundice, and splenomegaly, anesthetic agents and surgery can be very challenging because most anesthetic drugs are metabolized by the liver. Some hereditary

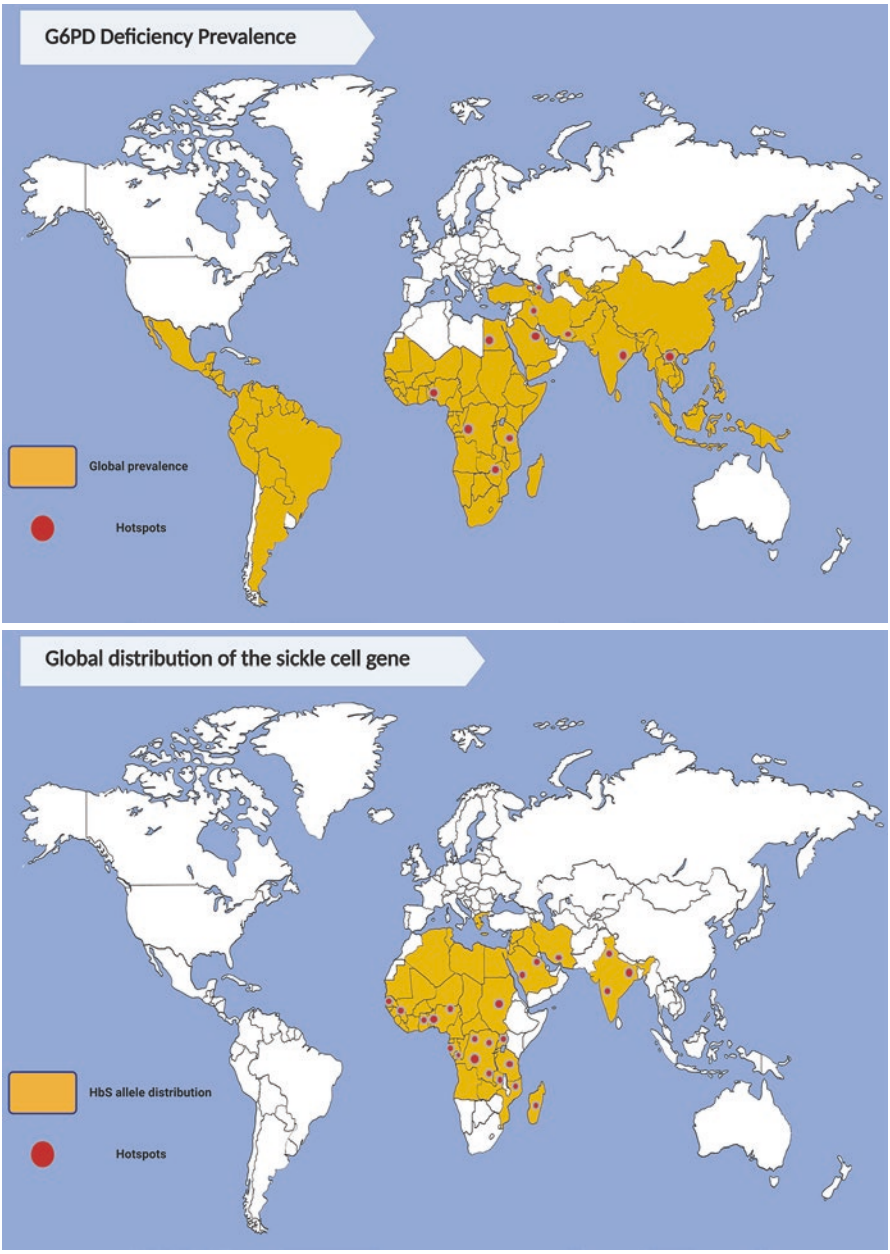

Fig. 11.1 Glucose-6-phosphate dehydrogenase (right) and sickle cell disease hot spot areas

spherocytosis (HS) case studies have reported that epidural and general anesthesia have the potential to decrease the liver's blood flow, which may lead to anesthesia-induced hepatotoxicity due to oxygen deprivation. It is highly recommended that preoperative anemia be rectified before any critical surgery (Gelman 1987). In cases of immediately necessary surgery, packed red cell transfusion can overcome the complication (Khatavkar et al. 2016).

Hemoglobinopathies

Sickle Cell Disease (SCD)

Sickle cell disease (SCD) is caused by a specific point mutation in the human β-globin (*HBB*) gene that results in the production of insoluble hemoglobin S (HbS). The severe form of SCD is called sickle cell anemia (Kato et al. 2018). More than 30 million people world-wide have SCD, with hotspots in Africa, the Middle East and central India (Tsaras et al. 2009). Hypoxia, alcohol, stress, cold weather, acidosis, and dehydration can trigger vaso-occlusive crises (VOC) in SCD patients. Preoperative assessment should review the hematological profile to avoid crises. Preoperative care for the SCD patient should combine the efforts of medical professionals, including surgeon, hematologist, anesthetist/anesthesiologist, and recovery room staff. Additionally, some major complications of SCD must be managed before surgery, including VOCs, chronic anemia, chronic pain, fever, infections, stroke, and pulmonary hypertension (Adjepong et al. 2018; Mangla et al. 2019). Some of the prophylactic measures for SCD include antibiotic prophylaxis, pneumococcal vaccination, thermoregulation, oxygenation and intravenous fluid administration. Also, there is a need for preoperative blood transfusion to reduce HbS to less than 30%. All of these considerations may help to manage complications (Hirst and Williamson 2001; Stanley and Christian 2013). Hydroxyurea primarily increases fetal hemoglobin (HbF) in SCD patients. This results in improvement of their signs and symptoms. But pharmacogenomic studies have shown that even the maximum tolerated dose (MTD) of hydroxyurea results in variable levels of HbF. Further investigations have shown that some single nucleotide polymorphisms (SNPs), in *HBG2*, *BCL11A*, and *HMIP* genes, can influence HbF levels following the consumption of hydroxyurea (Kolliopoulou et al. 2017; Yahouédéhou et al. 2018). Not only hydroxyurea effects are variable in these patients. Opioid medications such as codeine and hydrocodone, used in the management of VOC, elicit different responses because these drugs are converted to morphine and hydromorphone by cytochrome P450 2D6 (*CYP2D6* gene polymorphism). All in, pharmacogenetic and genome sequencing can play a significant role in the management of SCD (Iolascon et al. 2015; Kolliopoulou et al. 2017; Rampersaud et al. 2018). Choosing the correct anesthesia for SCD patients is complex and controversial because of differing studies. The determination of regional or general anesthesia should be based on the patient's underlying medical condition. It is crucial to select an anesthesia approach

that prevents and attenuates the vaso-occlusive episodes. Essentially, pain due to VOC should be distinguished from chronic sickle cell pain to ensure proper treatment (Bakri et al. 2015; Ghaffari et al. 2018). Neuraxial anesthesia has been advised over general anesthesia, due to its association with sympathectomy and vasodilation. It has, additionally, the potential to decrease vaso-occlusive episodes, but its drawbacks include headaches, hypotension, bradycardia (Khurmi et al. 2017).

Thalassemia

Thalassemia is a common microcytic hypochromic hemolytic anemia caused by mutations in the *HBB* or *human α-globin* (*HBA*) genes, resulting in decreased synthesis of affected globin chains. These mutations can partially or completely decrease the production of the affected globin. Thalassemia, mostly thalassemia major, is a challenge due to its severity and life-long requirement for constant care and blood transfusion (Naderi et al. 2013; Jahantigh et al. 2014; Needs and Lynch 2018). Regular blood transfusion leads to iron overload, which requires iron-chelating agents like deferoxamine, deferiprone, and deferasirox. Pharmacogenomic studies have shown that some patients have adverse drug reactions while some have none due to the UTG1A6 SNPs (Alizadeh et al. 2014; Iolascon et al. 2015). Further pharmacogenetic studies are being conducted on human pluripotent stem cells to find better treatment options for these patients (Suh 2017). Cutting-edge genome editing techniques—such as clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) and transcription activator-like effector nucleases (TALEN)—show promise in curing thalassemia (Finotti et al. 2015). Thalassemia patients are in a hypercoagulable state with increased platelet activation and aggregation, which makes them prone to thromboembolic events such as pulmonary embolism (PE), deep venous thrombosis (DVT) and portal vein thrombosis, or bleeding due to thrombocytopenia. In the case of surgery, in preoperative preparations, the use of procoagulants such as antifibrinolytics and factor concentrates should be limited unless a particular situation demands their use (Taher et al. 2008; Avery IV and Klick 2018). The anesthetist/anesthesiologist confronts some challenges in these cases: insufficient oxygen-carrying capacity due to severe anemia, difficulty in the airway due to extramedullary hematopoiesis, pulmonary hypertension, and diseases related to blood transfusion like hepatitis (Jyothi et al. 2015). Epidural anesthesia has been recommended to overcome some conditions, such as the need for postoperative mechanical ventilation due to the low capacity of RBCs to carry oxygen, and postoperative nausea and vomiting. In terms of decreasing oxygen need, epidural anesthesia is more satisfactory in enhancing the patient's recovery. In lowering the demand for neuromuscular blocking agents and intravenous analgesia, epidural anesthesia results in quicker awakening despite anemia and acidosis due to the anaerobic metabolism. In patients with a platelet count less than $100{,}000 \times 10^9$/L, the chance of bleeding is low. In such cases, regional anesthesia should be applied after evaluating risks and advantages (Huang et al. 2014; Govil et al. 2019).

Immune Hemolytic Anemia

Autoimmune hemolytic anemia (AHA) and Evans syndrome also can be obstacles to surgery. For the anesthetic management of these patients, hemodilutional autologous transfusion has been recommended as a useful measure to minimize complications related to bleeding and immune hemolytic reactions (Nagano et al. 2000; Igarashi et al. 2002; Soudabeh et al. 2014).

Aplastic Anemia

Aplastic anemia, associated with immunosuppression and pancytopenia, makes anesthetic management a challenge, particularly in pregnancy. Thrombocytopenia is a common complication in patients with aplastic anemia, which contraindicates regional anesthesia. General anesthesia seems to be the only option here (Table 11.1)

Table 11.1 Anesthetic considerations of erythroid disorders and hematological malignancies

Hematological diseases	Considerations and management
Glucose-6-phosphate dehydrogenase (G6PD) deficiency	1. Agents that may induce hemolysis in G6PD deficiency 1a. Anesthetic drugs: benzocaine, lidocaine, prilocaine, and articaine 1b. Oxidative agents: aminoquinolines, sulphur-containing antibiotics, rasburicase, high doses of aspirin, and paracetamol 2. Sevoflurane: temporary increase in the antioxidant defense system of cells
Hereditary spherocytosis (HS)	Anesthesia for patients with heredity spherocytosis may lead to anesthesia-induced hepatotoxicity, so it is imperative that anemia be rectified before hand
Sickle cell disease (SCD)	1. Pre-operative management of chronic anemia, chronic pain, fever, infections, fever, infections, stroke, and pulmonary hypertension 2. Prophylactic measures: antibiotic prophylaxis, vaccination, thermoregulation, oxygenation and intravenous fluids administration 3. Preoperative blood transfusion to reduce HbS to less than 30% 4. SNPs in genes (*HBG2, BCL11A, HMIP)* affect hydroxyurea function
Thalassemia	1. SNPs in *UTG1A6 gene* result in varying reactions to iron-chelating agents 2. Epidural anesthesia has been recommended because it comes with less stress and enhanced recovery 3. Platelet count less than 100,000 × 10^9/L comes with a low incidence of bleeding while using epidural anesthesia in these patients 4. Preoperative procoagulants such as antifibrinolytics and factor concentrates should be limited due to patient's hypercoagulable state

(continued)

Table 11.1 (continued)

Hematological diseases	Considerations and management
Autoimmune hemolytic anemia (AIHA) and Evans syndrome	Hemodilutional autologous transfusion has been recommended as a useful measure to minimize bleeding and immune hemolytic reactions
Ribavirin-induced acute hemolytic anemia	Patients with inosine triphosphatase (ITPA) deficiency are somehow protected against ribavirin-induced acute hemolytic anemia
Aplastic anemia	Thrombocytopenia contraindicates use of regional anesthesia
Nitrous oxide (N_2O)-induced anemia	Avoiding prolonged exposure to N_2O
Erythrocytosis	Preoperative hypoxia should be managed.
Von Hippel-Lindau (VHL) syndrome and Chuvash polycythemia	1. Presence of pheochromocytoma must be investigated before surgery 2. Regional and general anesthesia can be used, based on a VHL syndrome patient's condition, however, in cases with hemangioblastoma epidural blockades are limited.
Leukemia	1. Hyperleukocytosis (WBC > 100,000 × 10^9/L) and leukostasis syndrome is a serious complication before surgery 2. To avoid leukostasis syndrome, reduction of WBC before surgery seems necessary. Packed red cells should be transfused sparingly 3. Treating acute promyelocytic leukemia (APL) by ATRA+ arsenic trioxide (ATO) has a lower risk of developing thrombosis compared to ATRA 4. Blast crisis in patients with CML limits spinal or epidural anesthesia, because it might increase the risk of central nervous system (CNS) contamination by circulating blast cells 5. Infection, a major complication in leukemia, should be managed by supportive care and treatment of the underlying cause
Polycythemia vera (PV)	1. Hematocrit should be kept below 45% in men and less than 42% in women 2–4 months before surgery 2. Cytoreductive measures are usually used for high-risk patients 3. The bleeding diathesis in these patients requires careful use of regional anesthesia
Essential thrombocythemia (ET)	1. Reduction of the platelet count by cytoreductive therapy should be considered to overcome constant thrombocytosis 2. Regional anesthesia "especially spinal anesthesia" may cause spinal cord compression and paraplegia

(Marsh et al. 2009; Kaur et al. 2012a; Riveros-Perez et al. 2018). Propofol is a general anesthetic drug used for aplastic anemia patients (Ahmed and Monem 2005; Kaur et al. 2012b). Metabolism of propofol in the liver depends on several genes, including *CYP2E1, CYP2B6, CYP2C9, GSTP1, UGT1A9, SULT1A1* and *NQO1*, Disruption of these genes has the potential to alter the effect of propofol. Besides,

the underlying mechanism for propofol's action somehow depends on the *GAPAG2* receptor gene, and polymorphism of this particular gene may affect propofol anesthetic effects (Mikstacki et al. 2013, 2017).

Anemia Caused by Anesthetic Drugs

Anesthetic agents are one of several factors that can affect the RBC and its indices. For example, nitrous oxide (N_2O), known as laughing gas, has the potential to cause acquired megaloblastic anemia by irreversible inactivation of vitamin B12. Usually, prolonged exposure to N_2O can lead to the depletion of vitamin B12 and elevation of plasma homocysteine that are characteristics of B12 deficiency (Emmanouil and Quock 2007). This may make the patient vulnerable to cardiovascular disease (Duma et al. 2015; Ganguly and Alam 2015; Chi 2018). Interestingly, a comprehensive study on the medical staff who have been exposed to N_2O in for at least 5 years has demonstrated that N_2O gas can cause DNA damage. This study also compared the genotoxicity effects of sevoflurane and isoflurane with N_2O, which showed there is no genotoxicity related to sevoflurane and isoflurane (Wronska-Nofer et al. 2009).

Erythrocyte Recovery

In the matter of erythrocyte recovery, a study that compared the effects of epidural anesthesia, general anesthesia, and combination of both on red blood cell endogenous recovery showed that epidural anesthesia resulted in a higher rate of the circulating erythrocyte mass than general anesthesia or a combination (Borghi et al. 2005).

Polycythemia

Polycythemia or erythrocytosis is a condition related to an absolute increase in RBC mass, in which hemoglobin and hematocrit levels are above the normal range based on gender and age. This can be primary, where a genetic factor plays a role, or secondary, where the cause is non-genetic (McMullin 2008). Generally, secondary erythrocytosis follows hypoxia. Hypoxia during general anesthesia in surgery is a major clinical occurrence in which the response can range from mild hypertension and elevation in EPO to bradycardia.

Patients with pre-existing hypoxia should be identified and managed before surgery; conditions include respiratory disorders: chronic obstructive pulmonary disease (COPD); Pickwickian syndrome, cyanotic heart disease with right-to-left shunts, renal disorders and heavy smoking. Hemoglobinopathies with hypoxia

include high-affinity hemoglobins like Hb Yakima and methemoglobinemia. Hypoxia also can be a consequence of EPO administration, anabolic steroid use, and testosterone replacement therapy (Bendixen and Laver 1965; Tojo et al. 2015; Pillai and Babiker 2018). Often primary polycythemias such as polycythemia vera (PV) and Chuvash polycythemia have an underlying mutation in the erythropoiesis signaling pathway. Next, we should consider that the EPO level usually is normal in the primary type (McMullin 2008; Aljabry 2018). Mutation in the *von Hippel-Lindau* (*VHL*) gene leads to VHL syndrome and Chuvash polycythemia (Richard et al. 2002; Pastore et al. 2003; Perrotta et al. 2006). VHL syndrome is associated with spinal or retinal hemangioblastoma, renal cell carcinoma, or pheochromocytoma, a usually noncancerous tumor frequently occurring in the adrenal gland. For anesthetic management of the patient with VHL syndrome, the presence of pheochromocytoma must be considered. In such cases, epidural and general anesthesia can be used, based on patient condition, but in cases of hemangioblastoma, epidural blockades are limited (Murthy et al. 2006; Jalbani et al. 2015). Also, N2O cannot always be used for maintenance of anesthesia during surgery. For example, in a VHL case with cerebellar hemangioblastoma and renal cell carcinoma, N2O was avoided due to the possibility of carbon dioxide pneumoperitoneum; desflurane in a mixture of oxygen and air made that surgery uneventful (Sahni et al. 2019).

Anesthetic Considerations in Hematological Malignancies

Hematological malignancies such as leukemias, lymphomas, myeloproliferative neoplasms (MPN) and myelodysplastic syndromes (MDS) do not require surgery as such, but some situations require surgery and anesthetic management. Among them are infection, bone marrow (BM) biopsy or aspiration, chemotherapy and radiotherapy, orthopedic surgery, splenectomy, appendectomy, port implantation, and open-heart surgery. Such patients, especially children, are prone to infection due to immunosuppression, and in most cases require careful medical consideration. The collaboration of a skillful team of surgeons and medical oncologists is warranted. Since most hematological malignancies come with vast genetic variation, patients must be precisely evaluated and carefully managed before undergoing surgery (Spiers 1973; Hohenberger and Buchheidt 2005).

Leukemia

Anesthetic management and related therapy of leukemias should proceed carefully. Numerous genetic abnormalities can cause the different types of leukemia, making management of these patients more complex than most. Some leukemia patients develop anemia, coagulation disorders, immunosuppression or combinations

thereof. Moreover, the infiltration of blast cells into oropharyngeal tissue may lead to difficult intubation and/or pharyngeal hemorrhage. At times hyperleukocytosis (white blood cell (WBC) > 100,000 × 10^9/L) may trigger leukostasis syndrome, with acute respiratory failure and increased blood viscosity, which may cause bleeding and thrombosis (Naderi et al. 2014). Considering that surgery may induce this syndrome, the reduction of WBC before general anesthesia seems necessary. Importantly, packed red cells should be transfused sparingly, to avoid the development of the syndrome (Groeben et al. 1992; Giammarco et al. 2017).

Bleeding and thrombosis, especially in the acute leukemias, are considered major risk factors for early death. Acute promyelocytic leukemia (APL) induces a hypercoagulable state which should be carefully managed to avoid further complication. Anticoagulant therapy may put these patients at high hemorrhagic risk, which makes this therapy a challenge for managing APL. While, with the rise of all-trans retinoic acid (ATRA), APL has been largely managed, the rate of early hemorrhagic death has not significantly decreased; ATRA may play a role in promoting thrombosis (Rickles et al. 2007). However, treating patients with ATRA and arsenic trioxide (ATO) has a lower risk of thrombosis. In these patients, bleeding associated with disseminated intravascular coagulation (DIC) may occur. Cytoreductive therapy and supportive care such as platelets, fresh frozen plasma, cryoprecipitate, or fibrinogen concentrates are recommended to prevent bleeding (Thachil et al. 2015; Lad et al. 2017).

Chronic myeloid leukemia (CML) is an MPN that can occasionally proceed to blast crisis, with elevation of blast cells above 20%. Some studies suggest that spinal or epidural anesthesia be evaluated prior to use as it increases the risk of central nervous system (CNS) contamination by circulating blast cells (Owsiak and Bullough 2016; Rebahi et al. 2018).

Susceptibility to infection due to immunosuppression is a major obstacle among the many that challenge surgery in a leukemic patient, especially a child. This immunosuppression can be caused by BM dysfunction and/or treatment with steroids and radio- or chemo-therapy. While most infections are caused by gram-negative bacteria, patients are also prone to fungi like Aspergillus which affect patients undergoing chemotherapy, viruses such as cytomegalovirus (CMV) and Epstein–Barr (EBV) and parasites (Oduro-Dominah and Brennan 2013; Dong et al. 2019). Management consists of supportive care and treatment of the underlying cause. Patients, especially children, frequently have an indwelling central venous catheter (CVC). As a CVC can be a source of contamination it should be placed by a professional under aseptic conditions. One should ensure that these patients' surgeries are scheduled before surgery of any infective cases. The risk/benefit ratio of using regional anesthesia should be evaluated, since this kind of anesthesia, especially the neuraxial block, may also increase the risk of infection. Intramuscular injection might lead to formation of an abscess and should be avoided. Further, it is strongly recommended that patients be vaccinated against *S. pneumoniae, N. meningitidis,* and *H. influenzae* type b prior to procedures like splenectomy (Bonanni et al. 2017).

Polycythemia Vera and Essential Thrombocythemia

PV is an MPN, characterized by erythrocytosis, hyperviscosity and thrombocytosis and/or leukocytosis. Patients with PV are at increased risk of hemorrhagic events and/or thromboembolism (Gerds and Dao 2017). Although there is evidence of abnormal hemostasis in these patients, preoperative coagulation tests may be normal (Rigby and Leavell 1960). Keeping hematocrit below 45% by consumption of aspirin once or twice daily, with phlebotomy 2–4 months before surgery, is required to reduce thrombohemorrhagic complications. Cytoreductive measures for high-risk patients have been recommended, the main choice being hydroxyurea. Interferon-α, pipobroman, P-32 and busulfan are alternative options, because 20 and 25% of patients develop resistance to hydroxyurea (Sosis 1990; Sever et al. 2014; Tefferi and Barbui 2019). Adequate preoperative management of these patients, as enumerated above, minimizes complications, according to a comprehensive study which also noted that preoperatively uncontrolled patients and controlled patients had 36% and 5% mortality rates, respectively (Wasserman and Gilbert 1964). The bleeding diathesis in these patients mandates careful use of regional anesthesia (Sosis 1990; Saini et al. 2019). Another study found general anesthesia to be associated with more postoperative DVT than regional anesthesia in patients with PV (McKenzie et al. 1985).

Another MPN is essential thrombocythemia (ET), characterized by constant thrombocytosis with an inclination to thrombosis and hemorrhage (Brière 2007). Preoperative management of ET follows that of PV. In ET, reduction of the platelet count by cytoreductive therapy should be considered. Moreover, regional anesthesia, especially spinal anesthesia, should be managed carefully because it may cause a hematoma, which could lead to spinal cord compression and paraplegia (García-Ferreira et al. 2005; Sever et al. 2014; Tefferi and Barbui 2019).

Anesthesia and Hemostasis

One of the most common complications of surgical procedures is postoperative hypercoagulability. Major surgeries are associated with hypercoagulable and proinflammatory states which can continue into the postoperative phase. DVT and PE are among the most common coagulopathies of major surgical procedures, particularly lower-extremity vascular and orthopedic surgeries (Tuman et al. 1991; Christopherson et al. 1993; Rosenfeld et al. 1993). The exact underlying mechanism of the hypercoagulability remains unclear. Anesthesia and surgery, being stressful conditions, have significant effects on the hemostasis system. Hemostatic changes are due to several factors, including “stress response”, consumption of coagulation proteins at the site of injury, impaired synthesis, hemodilution and the effects of anesthesia on these proteins. Although surgery can increase acute phase reactants such as fibrinogen, FVIII, VWF and α-antiplasmin, many changes in the hemostasis

Table 11.2 Coagulation profile changes in patients undergoing major surgeries

	Surgery	Regional anesthesia	General anesthesia
Coagulation proteins	Fibrinogen	↑	↑
	Factor II	↓	↓
	Factor V	→	→
	Factor VIII	↑	↑[b]
	Factor X[f]	↓	↓
	Prekallikrein	↓[e]	↓[e]
Natural anticoagulants	Protein C	↓[a]	↓
	Protein S		
	Antithrombin-III	↓[c]	↓[c]
Fibrinolytic system	Plasminogen	↓	↓
	α-antiplasmin	↓[d]	↓[d]
	α2-macroglobulin	↓	↓
	α-antitrypsin	↑	↑
	PAI-1	→	↑
VWF	VWF	↑	↑[b]
D-dimer	D-dimer	→	→
Platelet	Platelet count	↑	↑[g]

VWF, von Willebrand factor; PC, Protein C; PS, Protein S; AT-III, Antithrombin-III; PAI-1, Plasminogen activator inhibitor-1

[a]Not significant: on day 7 the PC was significantly higher than preoperative value

[b]Although postoperative FVIII level is significantly high in both groups, this was significantly higher in generally anesthetized patients than regional anesthetized ones

[c]The maximum decrease (15–20%) was observed 3 h postoperatively

[d]Reached preoperative level on first postoperative day

[e]A continuous decrease was observed

[f]20% decrease

[g]Postoperative platelet count is significantly increased in both groups but this was significantly higher in generally anesthetized patients than regional anesthetized

system are triggered when the patient is anesthetized, even before surgery begins. This shows that both anesthetic and surgical stresses induce the changes (Table 11.2) (Collins Jr et al. 1977; Breslow et al. 1993; Rosenfeld et al. 1994).

Anesthesia and Thrombophilia

Perioperative thrombophilia is one of the main causes of morbidity and mortality in patients undergoing major surgery. Both acquired and inherited thrombophilia factors can increase the risk. Major surgery is associated with proinflammatory states that provoke hypercoagulability and, consequently, vaso-occlusive and thrombotic complications, as a major cause of surgery-related deaths.

Some perioperative changes such as elevated factor (F) VIII and von Willebrand factor (VWF) levels, decreased level of the natural anticoagulants such as heparin cofactor II, protein C and antithrombin, increased platelet function, and decreased fibrinolytic activities, can increase the risk of thrombosis (Ygge 1970; O'Brien et al. 1974; Collins Jr et al. 1977; Kluft et al. 1985; Andersson et al. 1987).

In a study on coronary artery disease (CAD), it is reported that in peoples who have A1A1 genotype the plasma FVIIa levels is epigenetically downregulated via methylation of F7 promoter. Hypo-methylation of F7 promoter in A1A1 genotypes increases the risk of CAD (Friso et al. 2012).

About the role of miR-223 in the thrombosis and atherosclerosis, it is suggested that hypo-methylation of miR-223 promoter increases the risk of atherosclerotic cerebral infarction (Rangrez et al. 2013; Li et al. 2017). Furthermore, hypermethylation of Thrombomodulin (TM) promoter correlates with the lower TM mRNA levels and higher plasma level of homocysteine and could be associated with increased risk of cerebral infarction (Yang et al. 2016).

The preoperative level of plasminogen activator inhibitor-1 (PAI-1) is a predictor for risk of postoperative thrombosis, while this is not true for fibrinogen. The plasma level of these proteins may differ between individuals, due to their unique genetic profiles. Due to normal gene variations, some patients may have higher levels, and be more prone to postoperative thrombotic events. The PAI-1 plasma level partly is regulated by the promoter guanidine insertion/deletion (4G/5G) polymorphism in the PAI-1 gene. Patients with PAI-1 4G/4G polymorphism are at higher risk of perioperative thrombosis (Dorgalaleh et al. 2013a). The FV Leiden and prothrombin G20210A mutations are among the most common gene variations and are associated with thromboembolic events (Table 11.3).

In fact, individuals with inherited thrombophilia are at lifelong risk of venous and arterial thrombosis, particularly in response to challenging situations such as pregnancy or surgery (Ogasawara et al. 2003; Hazirolan et al. 2004; Hosseini et al. 2015). Preoperative thrombophilia testing is not routine in patients without a history of thrombosis. The growing role of perioperative coagulation genomic in determining the risk of bleeding and thrombosis remains to be established (Morozowich et al. 2006). Cutting-edge technologies like NGS can help in developing the coagulation genomic, and improving personal anesthesia management of patients requiring surgery. The anesthetic considerations of thrombophilia range from perioperative use of prophylactic and/or therapeutic anticoagulation to major resuscitation following a PE (Kalantari et al. 2013; Gonzalez-Fiol and Eisenberger 2014). Regional anesthesia has a lower risk of thrombosis than general anesthesia (Hollmann et al. 2001). However, in patients receiving therapeutic anticoagulation, most regional anesthetics, particularly spinal and epidural anesthesia, are contraindicated (Gonzalez-Fiol and Eisenberger 2014).

FV Leiden, the most common inherited risk factor for venous thromboembolism (VTE), is more common in Scandinavian and northern European ethnicities, while rare in Asian and African populations (Dahlbäck 1995; Ornstein and Cushman 2003). Heterozygous carriers and homozygotes have a 4 in 10, and 100-fold increased risk of DVT, respectively (Cooley et al. 2007). For parturients with FV Leiden and

Table 11.3 Thrombophilic polymorphisms with potential adverse perioperative outcome

Polymorphism	Nucleotide change	Gene name	Gene symbol	Chromosomal location	Global MAF	Effect on plasma level of protein	Outcome
rs6050	Thr312Ala	Coagulation factor I	*FGB*	4q31.3	0.3292	–	Lysis-resistant fibrin, CTEPH risk factor Increases the risk of MI CES risk factor, Increases the risk of CHD
Bcl I Polymorphism					–	↑	
rs1800790	G455A				0.1598	↑	
rs1799963	G20210A	Coagulation factor II	*F2*	11p11.2	0.004591	↑	Thrombosis
rs3136516	A19911G				0.3058	↑	
rs6025	G1691A (FV Leiden)	Coagulation factor V	*F5*	1q24.2	0.005969	–	APCR phenotype Mild resistance to APC
rs1800595	A4070G (HR2)				0.0455	–	
rs6046	Arg353Gln (c.1238G>A)	Coagulation factor VII	*F7*	13q34	0.1341	↓	Thrombosis
rs3756008		Coagulation factor XI	*F11*	4q35.2	0.3315	–	Increases the risk of DVT
rs2036914					0.3678		
rs2289252					0.3343		
rs1801020	C46T	Coagulation factor XII	*F12*	5q35.3	0.4201	–	Increases risk of heart disease
rs5985	Val34Leu	Coagulation factor XIII A	*F13A1*	6p25.1	0.1478	–	Protective against thrombosis, recurrent pregnancy loss
rs2227589	G786A	Antithrombin III	*SERPINC1*	1q25.1	0.1253	↓	Increases the risk of DVT
rs1799809	A1641G	Protein C	*PROC*	2q14.3	0.4751	↓	Increases the risk of DVT
rs1799808	C1654T				0.3328	↓	

(continued)

Table 11.3 (continued)

Polymorphism	Nucleotide change	Gene name	Gene symbol	Chromosomal location	Global MAF	Effect on plasma level of protein	Outcome
A2001G, A2148G		Protein S	*PROS1*	3q11.1	–	↓	Increases the risk of DVT
A33G		Protein Z	*PROZ*	13q34	–	↓	Increases the risk of DVT
rs180113	C677T	Methylenetetrahydrofolate reductase	*MTHFR*	1p36.22	0.3246	–	Thermolability and decreased activity, HHC
rs1801131	A1298C				0.2277		
T833C, G919A		Cystathionine beta-synthase	*CBS*	21q22.3	–	–	Decreased activity, HHC
A2756G		5-methyltetrahydrofolate-homocysteine methyltransferase	*MTR*	1q43	–	–	Decreased activity, HHC
A66G		MTR reductase	*MTRR*	5p15.31	–	–	Decreased activity, HHC
C536T		Tissue factor pathway inhibitor	*TFPI*	2q32.1	–	–	Risk factor of thrombosis
G13A		Thrombomodulin	*THBD*	20p11.21	–	↓	Risk factor of thrombosis
rs1799889 (4G/4G)		Plasminogen activator inhibitor-1	*SERPINE1*	7q22.1	0.3600	↑	Increased risk of atherosclerosis and CHD Multiple Organ Dysfunction
rs1799768 (4G/5G)					0.4683	↑	
rs2020918; C7351T		Tissue plasminogen activator	*PLAT*	8p11.21	0.2824	↑	Risk factor of MI and stroke
C1040T		Thrombin-activatable fibrinolysis inhibitor	*CPB2*	13q14.13	–	–	Increased antifibrinolytic activity
rs4646994		Angiotensin I converting enzyme	*ACE*	17q23.3	–	–	Ischemic and hemorrhagic strokes
rs699	T704C	Angiotensinogen	*AGT*	1q42.2	0.2597	↑	Hypertension and thrombosis

CTEPH, chronic thromboembolic pulmonary hypertension; MI, myocardial infarction; CES, cardioembolic stroke; APCR, activated protein C resistance; DVT, deep vein thrombosis; HHC, hyperhomocysteinemia; CHD, coronary heart disease

spontaneous, induced or elective cesarean delivery under spinal or epidural anesthesia, it has been suggested that the underlying disease process, anticoagulant dosing alterations, and anesthetic options, be discussed early in the third trimester. Transition from low molecular weight heparin (LMWH) to unfractionated heparin (UH) must be done prior to the 38th gestational week (Harnett et al. 2005). However, the majority of data do not support the alteration of anesthesia technique in patients with the known FV Leiden genotype (Donahue 2004).

Protein C level is also decreased postoperatively. In addition to surgery-related protein C deficiency, its decreased level is observed as an inherited deficiency. Anesthetic management of patients with protein C deficiency include preoperative protein C replacement therapy with fresh frozen plasma (FFP), atraumatic procedure and provision of enough air leak around the endotracheal tube (Wetzel et al. 1986). Perioperative management of protein C deficiency has included the use of tailored atraumatic anesthetics, avoidance of tissue compression and dehydration, protein C replacement and anticoagulation (Kumagai et al. 2001; Batool et al. 2011; Tiwari et al. 2012). In protein S deficiency, any anesthetic technique can be used after protein S replacement therapy (Abramovitz and Beilin 1999; Sugimoto et al. 2018).

Several mutations are associated with methylenetetrahydrofolate reductase (MTHFR) deficiency, among which the C677T polymorphism is the most detrimental. Clinical manifestations of patients with MTHFR deficiency include neurological symptoms, cardiovascular and thromboembolic disorders (Gales et al. 2018). Anesthesiologist should avoid the use of N2O in patients with MTHFR deficiency (Shay et al. 2007). N2O irreversibly inhibits methionine synthesis and leads to decreased homocysteine re-methylation, thereby increasing systemic homocysteine, which increases the risk of thrombosis (Mayer et al. 1996; Badner et al. 2001). Such exposure also is associated with severe neurological and hematological manifestations. Hence, patients with MTHFR deficiency, especially homozygous patients, should not be anesthetized with N2O-containing general anesthesia and should be anticoagulated sufficiently whenever possible during their hospitalization. Spinal or epidural anesthesia can be considered except for patients receiving therapeutic anticoagulation. Thrombotic events in patients with MTHFR deficiency can cause kidney damage. Thus, one should consider altered drug clearance in patients receiving anticoagulants (Shay et al. 2007).

Antithrombin-III, the main physiological inhibitor of thrombin, while decreasing progressively during the early postoperative phase, more rapidly returns to the preoperative level following epidural rather than general anesthesia (Mayer et al. 1996; Corral et al. 2018). Both increased FVIII level and decreased antithrombin level can increase the risk of thrombosis. The risk is higher in patients with severe trauma. The antithrombin level was observed to fall up to 20% with both types of anesthesia. This degree of decrease can increase thrombosis risk four-fold (Konkle et al. 2003; Martinelli et al. 2014; Jooste et al. 2019).

Inherited antithrombin deficiency is the strongest risk factor for thrombosis, which presents in up to 1% of patients with venous thrombosis. Up to 80% of patients with antithrombin deficiency have SERPINC1 gene defects (Martinelli

et al. 2014; Corral et al. 2018). There are no randomized clinical trials, guidelines or consensus statements about the use of antithrombin concentrate. However, a randomized, double-blind, placebo-controlled trial demonstrated that supplementation of antithrombin improves heparin sensitivity during cardiopulmonary bypass in infants (Jooste et al. 2019). According to the case reports and series, general or regional anesthesia management of anesthesia in patients with antithrombin deficiency includes perioperative use of recombinant or hemoderivative antithrombin, placement of a filter in the inferior vena cava to prevent PE, active mobilization of lower extremities and perioperative anticoagulation (Konkle et al. 2003; Okamoto and Minami 2003; Pamnani et al. 2010; Piper and Farrell 2015; Yu et al. 2018). In some patients, decreased levels of antithrombin-III and protein C were sufficient for spontaneous thrombosis, as can be observed in patients with inherited deficiencies of these factors (Martinelli et al. 2014; Corral et al. 2018). Antithrombin-III and α-antiplasmin are sensitive indices of coagulation and activation of fibrinolysis, respectively (Konkle et al. 2003; Pamnani et al. 2010; Jooste et al. 2019). Multiple studies to date have unequivocally demonstrated that regional anesthesia, particularly epidural anesthesia, can ameliorate postoperative hypercoagulability. In a study on 20 premenopausal women undergoing abdominal hysterectomy, FVIII and VWF levels were observed to be lower in epidural than general anesthesia (Bredbacka et al. 1986). Several randomized clinical or controlled trials on patients with lower-extremity vascular reconstruction, total hip replacement, and abdominal hysterectomy, demonstrate that epidural anesthesia can improve fibrinolytic activity by hindering the postoperative release of PAI-1 protein (Simpson et al. 1982; Modig et al. 1983; Donadoni et al. 1989; Rosenfeld et al. 1993). Fibrinolytic activity is increased, and surgery related "stress response" is reduced, by epidural anesthesia. Surgical stress, with significant adrenocortical response, can increase fibrinolytic activity, while epidural anesthesia can decrease fibrinolysis by decreasing adrenocortical response (Rosenfeld et al. 1993). When a long-acting local anesthetic such as bupivacaine is used, in combination with adrenaline and ephedrine, it can increase fibrinolytic activity. Even a small amount of adrenaline can increase fibrinolytic activity (Rosenfeld et al. 1993). A study on the flow of blood in the calf during total hip replacement, using venous occlusion plethysmography (VOP) on the non-operated leg, demonstrated that generally anesthetized patients had significantly lower blood flow and venous capacity in the lower limb at the end of surgery than another group with epidural blockade. It suggested that a constant decrease of the blood flow in the deep veins of the lower limbs may increase the risk of DVT (Modig et al. 1980). Absorption of local anesthetic agents from the epidural space has systemic effects such as direct impairment of platelet aggregation (Feinstein et al. 1976; Borg and Modig 1985; Henny et al. 1986). Patients who were given general anesthesia and a postoperative epidural infusion of bupivacaine-fentanyl showed a nine-fold decreased incidence of vascular graft occlusion than patients with general anesthesia and patient-controlled opioid analgesia (PCA) (Tuman et al. 1991). Patients

undergoing peripheral vascular surgery under epidural anesthesia had five-fold lower need for reoperation due to graft failure than patients who were given general anesthesia (Christopherson et al. 1993). An equivalent decrease in thromboembolic events has been observed in patients who had knee arthroplasty, or open prostatectomy, under epidural anesthesia (Hendolin et al. 1981; Jørgensen et al. 1991).

Furthermore, the use of anticoagulants, antiplatelets, and fibrinolytic drugs has a great effect on the perioperative VTE. The simultaneous use of regional anesthesia and antithrombotic agents may increase the risk of bleeding. In a patient with a known coagulopathy, anesthesiologists encounter challenging situations that require risk/benefit decision-making. Any coagulopathy is a challenge for regional anesthesia as it may cause serious complications.

Fibrinogen levels remain increased for a relatively long time (7 days) after major surgeries. Fibrinogen, FVIII and VWF levels are increased postoperatively. Although this increase can be observed in general and regional anesthesia, the FVIII and VWF level increase is significantly higher in general versus regional anesthesia. This increase is attributed to beta-adrenergic receptors; epidural anesthesia can attenuate this increase (Rosenfeld et al. 1993).

Epidural anesthesia can improve the blood flow in the lower extremities, while general anesthesia decreases this flow in the deep veins and can increase the risk of graft occlusion. Postoperative arterial thrombosis is higher in patients with a higher preoperative level of PAI-1 under general anesthesia. The postoperative PAI-1 level is higher in regional than general anesthesia. The rate of arterial thrombosis is higher in patients under general than regional anesthesia. Impaired fibrinolysis may relate to postoperative arterial thrombosis. It seems that regional anesthesia combined with epidural fentanyl analgesia may decrease the risk of arterial thrombosis due to lower PAI-1 levels in patients with lower extremity revascularization (Rosenfeld et al. 1993). PAI-1, a specific, rapidly acting inhibitor of tissue- (tPA) and urokinase-plasminogen activators (uPA), is primary regulator of plasminogen. PAI-1 deficiency and increased levels are associated with bleeding and thrombosis, respectively (Rosenfeld et al. 1993). Regional anesthesia attenuates surgery-related cortisol and catecholamine response, which change is suggested as main cause of a number of hemostatic changes under general and regional anesthesia. Dexamethasone administration can increase the PAI-1 level and impair fibrinolysis function (Rosenfeld et al. 1993; Corral et al. 2018). Increased PAI-1 level is also associated with the risk of myocardial infarction (MI).

Perioperative morbidity and mortality is higher in patients receiving general rather than regional anesthesia, while incidence of postoperative DVT is lower in patients with regional rather than general anesthesia. Increased levels of coagulation factors are smaller in patients receiving general rather than regional anesthetic.

A meta-analysis of randomized control trials demonstrated that neuraxial blocks decrease death by 30%, DVT by 44%, and PE by 55% (Modig et al. 1983; Bredbacka et al. 1986).

Anticoagulation Therapy and Anesthesia

Anesthetic Considerations for Patients Receiving Fibrinolytic Therapy

Fibrinolytic drugs can cause severe bleeding, especially in invasive procedures. Neuraxial hemorrhage can be observed in patients undergoing heparin and/or antiplatelet therapy. Patients with a history of lumbar puncture, epidural or spinal anesthesia and concomitant steroid injection into the epidural space should be closely monitored. Patients receiving thrombolytic drugs should not undergo puncture of a non-compressible vessel within 10 days after surgery. Patients undergoing fibrinolytic therapy should not receive epidural or spinal anesthesia, except under specific circumstances. Should patients receive concurrent neuraxial blocks and thrombolytic agents, evaluation of their neurologic status every two hours during surgery is recommended. Epidural catheter infusions must be restricted to medications inhibiting the risk of sensory and motor block to ensure better monitoring of neurological status. Unforeseen requirements for thrombolytic drugs may arise in patients with a neuraxial catheter. There is no clear-cut recommendation for catheter removal in such situations. However, fibrinogen assay can determine remaining fibrinolytic activity and the appropriate time for catheter removal (Horlocker et al. 2019).

Anesthetic Considerations for Patients on Unfractionated Heparin (UFH)

The medical history of patients should be reviewed to determine the possible use of coagulation modifiers. Two- or three-time daily thromboprophylaxis administration of 5000 U (low-dose) UFH is not contraindicated with the neuraxial techniques, if anesthesia is administered 4–6 h after heparin administration. Patients with a UFH dose greater than 10,000 U have an increased risk of surgical bleeding. However, the safety of neuraxial blockade for patients with daily or twice-daily administration of UHF has not been determined. Hence, risk-benefit assessment of use of UHF three times per day should be evaluated individually. However, in pregnant patients receiving preoperative thromboprophylaxis of high-dose (7500–10,000 U) UFH, daily or twice-daily dose no more than 20,000 U, neuraxial blockade is recommended to be administered 12 h after subcutaneous heparin administration, after evaluation of the patient's hemostatic state. In preoperative administration of high-dose (more than 10,000 U per dose or total >20,000 U daily) UFH in pregnant patients, it is recommended that neuraxial blockade be administered 24 h after the subcutaneous heparin administration. Due to the higher risk of heparin-induced thrombocytopenia (HIT) in patients with more than 4 days of heparin therapy, a platelet count is recommended prior to catheter removal and the neuraxial blockade.

Some specific issues are recommended for patients anesthetized with neuraxial techniques and concomitant administration of intravenous heparin, including:

1. Patients with other coagulopathies should not be anesthetized with neuraxial techniques.
2. There must be a one-hour delay in heparin administration, after needle positioning.
3. Neuraxial catheters should be removed 4–6 h after administration of the last heparin dose, with resumption of heparin administration one hour after catheter removal.
4. For rapid recognition of a motor blockade, the continuous post-operative state of patient stability should be recorded. The lowest concentration of regional anesthetics should be administered to promote immediate diagnosis of a spinal hematoma.
5. When needle positioning is difficult and/or accompanied by hemorrhage, discontinuing neuraxial anesthesia is recommended. In this situation, a suitable risk-benefit decision should be made by the surgeon and anesthesiologist. It is unclear whether the risk of neuraxial hematoma is increased while the anesthetic is accompanied by full anticoagulation. Postoperative monitoring of neurological function is recommended and decision-making about the type of analgesia should minimize the degree of sensory and motor blockade, yielding a subsequently easy recognition of unexpected neuro-difficulties (Table 11.4) (Horlocker et al. 2019).

Table 11.4 Management of neuraxial anesthesia in patients on antithrombotic or thrombolytic therapy

Drug	Recommended time interval between cessation of drug and neuraxial puncture	Recommended time interval between catheter removal and re-administration of drug	Description
• Fibrinolytic agents	...	…	• There is no definitive recommendation. However, at least 48 h time-interval between cessation of drug and neuraxial puncture and between catheter removal and re-administration of drug is suggested. After this time-interval it is suggested to measure fibrinogen level to ensure normalization of coagulation
• IV UFH (prophylactic and therapeutic)	4–6 h	1 h	• Normalization of coagulation state should be verified before neuraxial puncture • Residing neuraxial catheter should be removed 4–6 h after the last dose of heparin and after verification of normalization of coagulation

(continued)

Table 11.4 (continued)

Drug	Recommended time interval between cessation of drug and neuraxial puncture	Recommended time interval between catheter removal and re-administration of drug	Description
• Low-dose SC UFH for prophylaxis (5000 U)	4–6 h	1 h	• Residing neuraxial catheter should be removed 4–6 h after low-dose SC UFH administration
• High-dose SC UFH for prophylaxis	12 h	…	• The safeness of catheter removal in patients receiving high-dose SC UHF (>5000 U) has not been guaranteed. Risk/benefit decision making should be done on a personalized basis
• SC therapeutic UFH	24 h	…	…
• Prophylactic LMWH	12 h	4 h	• In patients receiving once- or twice- daily prophylactic dosing of LMWH post-operatively, the first dose must be given at least 12 h after the needle or catheter positioning, provided that there is sufficient hemostasis. In patients receiving single-daily prophylactic dosing of LMWH, the second dose should not be given earlier than 24 h after the first dose and the catheter must be removed 12 h after the last dose
• Therapeutic LMWH	24 h	4 h	• In patients receiving therapeutic doses of LMWH, monitoring of anti-factor Xa activity level should be considered, especially in senile patients and patients with renal dysfunction
• Fondaparinux	3–4 days	24 h	…

Table 11.4 (continued)

Drug	Recommended time interval between cessation of drug and neuraxial puncture	Recommended time interval between catheter removal and re-administration of drug	Description
• Warfarin (chronic therapy)	5 days	…	• INR should be normalized before the neuraxial technique • In patients on low-dose warfarin therapy during epidural technique daily monitoring of INR is recommended • When patients begin warfarin therapy less than 24 h prior to the surgery, neuraxial blockade depends on the normalization of INR • Removal of neuraxial catheter is limited to INR<1.5 in patients who receive warfarin for thromboprophylaxis. Although removal of the epidural catheter 12–24 h after warfarin administration seems to be uneventful, the risk of epidural catheter removal after 48 h is not guaranteed
• Direct anti-FXa agents	3 days	6 h (This time is 5 h for Betrixaban)	• Neuraxial puncture earlier than 3 days should be limited to consideration of anti-factor Xa activity levels
• Dabigatran	5 days	6 h	• Recommended time interval between cessation of dabigatran and neuraxial puncture according to the values of creatinine clearance rate is recommended.
• NSAIDs	Whenever	Whenever	• There is neither additional risk for spinal hematoma in patients having neuraxial anesthesia, nor particular worry about the scheduling of catheter removal

(continued)

Table 11.4 (continued)

Drug	Recommended time interval between cessation of drug and neuraxial puncture	Recommended time interval between catheter removal and re-administration of drug	Description
• Ticlopidine	10 days	24 h	• The re-administration of thienopyridine derivatives and ticagrelor following needle positioning or catheter removal is limited to the lack of an initial higher dose of thienopyridine derivatives and ticagrelor given at the beginning of a course of treatment. If a loading dose is given, a time interval of 6h between catheter removal and thienopyridines is recommended
• Clopidogrel	5–7 days	24 h	
• Prasugrel	7–10 days	24 h	
• Ticagrelor	5–7 days	24 h	
• Abciximab	1–2 days	…	• Although the administration of GPIIb/IIIa antagonists is contraindicated until 4 weeks after surgery, it is recommended that while neurological functionality is monitored, the GPIIb/IIIa antagonists be administered simultaneously in the postoperative phase. Timing of catheter removal is based on ongoing risk of thromboembolism and need for continued antithrombotic therapy and the potential for spinal bleeding
• Eptifibatide	4–8 h	…	
• Tirofiban	4–8 h	…	
• Cilostazol	2 days	6 h	…
• Dipyridamole	1 days	6 h	
• Cangrelor	3 h	8 h	
• Herbal medication	Whenever	Whenever	• Garlic, ginkgo and ginseng are not associated with additional risk of spinal hematoma in patients undergoing epidural or spinal anesthesia and will not interfere with performing neuraxial blockade

IV UFH, intravenous unfractionated heparin; SC UFH, subcutaneous unfractionated heparin; LMWH, low molecular weight heparin; NSAIDs, nonsteroidal anti-inflammatory drugs; h, hour

Anesthetic Considerations for Patients on Low Molecular Weight Heparin (LMWH)

The current recommendations are not capable of entirely eradicating the possibility of spinal hematoma. Patients receiving chronic anticoagulation therapy via high-dose LMVH are at high risk of destabilization of their coagulation state. Despite the advantages of monitored high-dose LMWH therapy, measurement of plasma levels of anti-FXa is not a good predictor of bleeding risk. No residual anti-FXa level ensures a safe neuraxial blockade. Concomitant administration of antiplatelet agents, dextran, or other oral anticoagulants to a patient with LMWH may increase the risk of spinal hematoma. Due to the risk of HIT in patients with more than 4 days of LMWH therapy, a platelet count is recommended prior to catheter removal.

In a patient receiving preoperative prophylactic doses of LMWH, needle positioning should be done no earlier than 12 h after the LMWH administration. Delaying surgery is not necessarily recommended in bloody needle and catheter positioning. In this situation, the surgeon should be consulted and postoperative re-administration of LMWH postponed for 24 h. In patients receiving a high dose of LMWH, it is recommended that needle insertion be postponed at least 24 h after administration of LMWH to ensure the optimal hemostasis status. The monitoring of remaining anti-FXa activity should be considered, especially in senile patients and those with renal dysfunction For general surgery, the recommendation is against the use of neuraxial techniques if patients have received LMWH 2 h preoperatively. Due to maximum antithrombotic activity in this interval, needle positioning might be accompanied with a high bleeding tendency.

Enoxaparin is used for the management of patients with DVT or PE. For enoxaparin, positioning or removal of a neuraxial catheter must be postponed for no less than 12 h following administration of a prophylactic dose. For patients receiving therapeutic doses, the time interval should be 24 h. A postoperative dose of enoxaparin should be administered 4 h following catheter removal (Horlocker et al. 2019).

Anesthetic Considerations for Patients on Fondaparinux

Fondaparinux is a synthetic pentasaccharide that can selectively inhibit FXa. This anticoagulant can be used after extensive orthopedic surgery, or the management of PE (Turpie et al. 2002; Matisse Investigators 2003). Available data about the risk of spinal hematoma related to the administration of fondaparinux and its postoperative initial dosing are insufficient. The recommendations are against the administration of fondaparinux in patients with a residing epidural catheter. The recommended time-interval between interruption of fondaparinux and the pain blockade process is 3–4 days. The recommended time-interval between the pain blockade process and re-administration of fondaparinux is 24 h (Narouze et al. 2015).

Anesthetic Considerations for Patients on Oral Anticoagulants

Warfarin

Contrary to the achieved adequate FVII activity observed by decreasing INR, hemostatic conditions (FII and X activity levels) may not be enough to prevent hemorrhage during the first 24–72 h after interrupting a durable warfarin therapy (Xi et al. 1989; Ansell et al. 2008). Thus, care must be taken when a patient with interrupted durable warfarin therapy has to undergo a neuraxial technique. It is recommended that the surgical procedure be performed preferably 5 days after interruption of the durable warfarin therapy; initiation of the neuraxial blockade depends on the normalized INR. Recommendations are against the simultaneous administration of other oral anticoagulants with warfarin, the effects of which may not be reflected in INR (such as non-steroidal anti-inflammatory drugs (NSAIDs), UHF, LMWH and thienopyridine derivatives) but that affect the other coagulation mechanisms. At the beginning of warfarin therapy, less than 24 h prior to surgery, the neuraxial blockade should be accompanied by regular monitoring that INR is at the normal level. Daily INR checking is also suggested during the epidural analgesia for patients receiving low doses of warfarin. The neurological functions of patients receiving warfarin therapy should be monitored regularly during the epidural analgesia. Decision on the type of analgesia should strive to minimize the degree of sensory and motor blockade. In patients receiving prophylactic doses of warfarin, removal of neuraxial catheters should be limited to those with an INR of 1.5 and lower (activity of coagulation factors is considered to be more than 40%). Epidural catheter removal the first 12–24 h after administration of warfarin is not associated with increased risk of bleeding. However, epidural catheter removal at 48 h is not safe enough. It seems helpful to patients with an INR between 1.5 and < 3 to surgically remove a residing catheter. The administration history of other modulators of hemostasis that may have no effect on the INR (clopidogrel bisulfate, LMWH, UHF, aspirin and other NSAIDs) also should be checked. It is suggested that the neurological function form be monitored until the desired INR is achieved, before catheter removal. In patients undergoing neuraxial catheter infusion with an INR 3 or higher, it is strongly recommended that warfarin administration be reduced or suspended, because there is no reliable advice for simplifying catheter removal in these patients (Horlocker et al. 2019).

Genetic-Guided Dosing of Warfarin

Some evidence indicates that genetic-based differences in the warfarin metabolism could affect the functionality of the drug. For instance, CYP2C9 (cytochrome P450 family 2 subfamily C member 9) is a polymorphic gene which encodes a monooxygenase involved in the metabolization of more potent enantiomer of warfarin (S-warfarin) (Ansell et al. 2008). The more prevalent and well-investigated alleles

of this enzyme are 2C9*2 (rs1799853: C430T) and 2C9*3 (rs1057910: A1075C) which have impact on pharmacokinetics of warfarin. Carriers of such alleles have reduced capacity to metabolize S-warfarin, resulting in reduced warfarin requirement compared to people with wild-type enzyme (2C9*1) (Ansell et al. 2008). Warfarin plays its anticoagulant role by inhibiting the vitamin K epoxide reductase (VKOR) enzyme in the vitamin K cycle. There are several variants of VKORC1 gene producing enzymes with different impacts on the pharmacodynamics of warfarin. For example, the H1 and H2 haplotypes are warfarin-sensitive and the H7, H8, and H9 represent warfarin-resistant haplotype (Ansell et al. 2008). The polymorphism of G3673A (rs9923231) is in the promoter region of VKORC1 gene affecting the pharmacokinetics of warfarin. The carriers of A allele have lower expression and activity of the VKOR enzyme. The A allele is more common in Asian populations. This issue provides an explanation for lower doses of warfarin in individuals of Asian descent. G9041A (rs7294) is a SNP in the 3′UTR of VKORC1 gene and it might be correlated with higher doses of warfarin (Owen et al. 2010).

Direct Oral Anticoagulants (DOACs)

Direct Oral FXa Inhibitors

Direct FX inhibitors, including rivaroxaban, apixaban, edoxaban, and betrixaban, have a growing role in the management of patients with thromboembolic disorders. Neuraxial blockade is recommended to be done 3 days after interruption of direct anti-FXa agents. Earlier than 3 days, the blockade should be done after considering anti-FXa activity level. However, an allowable level of remaining anti-FXa activity to be reached before administering neuraxial blockade remains unspecified. The catheter must be removed 6 h before the first postoperative dose of direct anti-FXa agent. This time interval is 5 h for betrixaban. Recommendations are against implementation of neuraxial blockade in patients with betrixaban therapy and a creatinine clearance (CrCl) rate of less than 30 mL/min. In patients with a residing catheter and an unexpected requirement for anti-FXa agents, it is recommended to that the agents be administered in a specific time interval (rivaroxaban 22–26 h, apixaban 26–30 h, edoxaban 20–28 h, and betrixaban 72 h) or after a calibrated anti-FXa assay prior to the catheter removal has been performed (Horlocker et al. 2019).

Direct Oral Thrombin Inhibitors

The renal clearance of dabigatran may be affected by surgery. It is recommended that the neuraxial blockade be done 5 days after discontinuation of dabigatran. For shorter intervals, patients should be checked by dilute thrombin time (dTT) and

ecarin clotting times (ECT). An allowable level of remaining dabigatran activity, before receiving neuraxial blockade, remains unspecified. In patients with a residing catheter and an unexpected need for dabigatran, it is recommended to dabigatran dosing be held for 34–36 h, or that dTT and ECT be evaluated, prior to the catheter removal. Patients receiving parenteral thrombin inhibitors, including desirudin, bivalirudin, and argatroban, should not use neuraxial anesthetics (Horlocker et al. 2019).

Anesthetic Considerations for Patients on Antiplatelet Drugs

The antiplatelet drugs such as aspirin, platelet adenosine diphosphate receptor (P2Y12 subtype) antagonists (thienopyridine derivatives): clopidogrel, ticlopidine and prasugrel; GPIIb/IIIa antagonists: tirofiban, eptifibatide and abciximab; have different effects on platelet function. Bleeding time as a monitoring test of platelet function is not reliable. Thus, preoperative monitoring of patients receiving antiplatelet therapy is mandatory to minimize the risk of bleeding. Clinical manifestations, including petechiae, purpura, mucosal bleeding and easy bruising, also should be considered. The NSAIDs like aspirin appear to be associated with no additional risk of spinal hematoma in patients undergoing spinal or epidural anesthesia. There is no interference with neuraxial blockade in patients receiving NSAIDs. Also, there is no particular worry about the scheduling of catheter technique, monitoring of neurological functionality or the scheduling of catheter removal. The recommendations are against the implementation of neuraxial techniques in patients receiving NSAIDs with possible concomitant administration of antithrombotic drugs such as LMWH, UFH and oral anticoagulants at the initial time after surgery. Cyclooxygenase-2 (COX2) inhibitors such as celecoxib, etoricoxib and rofecoxib have a slight impact on platelet function; only concomitant administration with antithrombotic drugs might considerably increase the effect.

It is recommended that neuraxial blockade be performed 10 days after stopping ticlopidine, 5–7 days after clopidogrel, and 7–10 days after prasugrel. Twenty-four hours post-operative re-administration of thienopyridine derivatives is suggested. When neuraxial blockade is required 5–7 days after discontinuation of clopidogrel, platelet function should be reassessed to ensure elimination of drug effects on the platelets. The recommendations are against a sustained neuraxial catheter in patients receiving prasugrel or ticagrelor, because the drugs are quick-onset and do not require long-term catheterization. Due to the notion that both ticlopidine and clopidogrel are slow-onsets, a sustained neuraxial catheter might be kept for 24–48 h if an initial higher dose of antiplatelet medication is not given at the beginning of treatment. The re-administration of thienopyridine derivatives and ticagrelor following needle positioning or catheter removal is limited to the lack of an initial higher dose of thienopyridine derivatives and ticagrelor given at the beginning of a course of treatment. If not, it is recommended that the catheter be removed 6 h after

re-administration of thienopyridine derivatives and ticagrelor. It is recommended that neuraxial blockade be performed 5–7 days after interruption of ticagrelor therapy.

The neuraxial blockade in patients receiving platelet GPIIb/IIIa inhibitors should be limited to a time in which the drug effects have been eliminated and platelet aggregation has recovered. Time duration for abciximab is 1–2 days, and for eptifibatide and tirofiban 4–8 h. Although the administration of GPIIb/IIIa antagonists is contraindicated until 4 weeks after surgery, it is recommended that neurological functionality be monitored, and the GP IIb/IIIa antagonist be administrated simultaneously during the postoperative phase.

Cilostazol is a platelet aggregation inhibitor with vasodilating properties that selectively inhibits the phosphodiesterase type 3. Due to the lack of a known risk of bleeding related to neuraxial blockade in a patient receiving cilostazol, it is recommended to apply a 2-day interval between the neuraxial blockade and cilostazol interruption. Re-administration of the first postoperative cilostazol dose should be done 6 h after catheter removal.

Dipyridamole and cangrelor are platelet aggregation inhibitors that inhibit the P2Y12 receptor. The risk of bleeding related to neuraxial blockade in patients receiving cangrelor is unclear. Concomitant administration of dipyridamole with aspirin might increase the risk of hemorrhage. According to the drug's half-life, it is recommended to wait 24 and 3 h between neuraxial blockade and interruption of the dipyridamole and cangrelor, respectively. Re-administration of the first postoperative dipyridamole and cangrelor dose should be done 6 and 8 h after catheter removal, respectively (Horlocker et al. 2019).

Anesthetic Considerations for Patients on Herbal Medications

Plants with medicinal properties such as garlic—reduction of blood pressure and inhibition of platelet aggregation; ginkgo—inhibition of platelet-activating factor; and ginseng—prolongation of thrombin time and partial thromboplastin time in animals (Horlocker et al. 2003) seem not to be associated with additional risk of spinal hematoma in patients undergoing epidural or spinal anesthesia. Nor will they interfere with neuraxial blockade (Horlocker et al. 2019).

Anesthetic Considerations for Patients with Underlying Bleeding Disorders

Patients with congenital bleeding disorders require special precautions to reduce the risk of perioperative bleeding (Tabibian et al. 2016; Naderi et al. 2018). VWD is the most common congenital bleeding disorder with estimated incidence of 1% in the

general population. The disorder is more common in some populations such as the Swedes. The disorder can be considered a potential risk factor for anesthesia. Most patients with VWD are affected by VWD type 1, diagnosis of which is challenging. Although molecular analysis of the VWF gene could be used for precise diagnosis, it is time-consuming and laborious. Most anesthetic recommendations are for patients with hemophilia, not for other rare or common congenital bleeding disorders (Dorgalaleh et al. 2018a, b). In fact, perioperative bleeding is a significant risk factor in all patients with congenital bleeding disorders, even in patients with mild disorders such as FXI deficiency and combined FV and FVIII deficiency (Dorgalaleh et al. 2016, 2017; Naderi et al. 2016; Tabibian et al. 2016; Bamedi et al. 2017) (Tables 11.5 and 11.6).

For anesthetic management of patients with bleeding disorders, pre-operative administration of deficient coagulation factor should be considered. For instance, one anesthetic consideration for patients with hemophilia A is preoperative administration of hemoderivative or recombinant FVIII to increase the plasma FVIII level. The recommendations are against the administration of NSAIDs in hemophilia patients due to the increased risk of hemorrhage. Hemophilia patients who are supposed to undergo a lumbar puncture should first be managed with a hemoderivative or recombinant coagulation factor to restore coagulation factor activity. Hemophilia patients with active pharyngeal bleeding are exposed to risk of airway obstruction resulting from unsafe airway protection, even with administration of FVIII concentrate. Hence, elective mechanical ventilation provided by insertion of an endotracheal tube into the airway is helpful to avoid airway obstruction. Recommendations for post-operative pain management of patients with hemophilia are against the intramuscular injection of analgesia. Pre-operative evaluation of hemophilia patients must involve inhibitor screening and assay, if resumed plasma factor activity level is less than anticipated. About the timing of surgery it is better to be scheduled at the start of the week, and first of the day, for the best laboratory and blood bank support, if needed. The dosing regimen and duration of coagulation factor concentrate coverage, depending on the type of surgery, should be enough to maintain levels until the postoperative phase (Membership of the Working Party et al. 2013). In patients with hemophilia who generate antibody against FVIII in response to given hemoderivatives, administration of recombinant products is indicated (Membership of the Working Party et al. 2013). Generally, it is suggested that if a patient with an investigated coagulation malfunction is supposed to be anesthetized via a regional technique, an anesthesiologist expert in this field should conduct the process. This is probably because an expert regional anesthesiologist will require fewer tries to reach the successful blockade (Membership of the Working Party et al. 2013).

A meta-analysis of randomized control trials revealed that neuraxial blockade reduces postoperative bleeding requiring transfusion and preoperative blood transfusion > 2 blood units.

FXII deficiency, or Hageman deficiency, is a relatively common autosomal recessive coagulopathy. The estimated incidence of the disorder is 1.5–3% in the general population. Patients with FXII deficiency do not have a bleeding tendency,

Table 11.5 Characteristics of congenital bleeding disorders

Factor deficiency	Subtype	Gene	Inheritance	Incidence	Diagnosis	Therapeutic choice	Clinical manifestations
FI deficiency	Afibrinogenemia	*FGA, FGB, FGG* (4q28)	AR	1/1,000,000	PT: P APTT: P TT: P RT: P Fibrinogen activity: UD Fibrinogen antigen: UD	FFP Cryoprecipitate Pd fibrinogen	UCB Epistaxis Thrombotic events Menorrhagia Hemarthrosis Gingival bleeding Postoperative bleeding CNS bleeding
	Hypofibrinogenemia		AD	UD	PT: P APTT: P TT: P RT: P Fibrinogen activity: <1.5 g/L Fibrinogen antigen: <1.5 g/L Fibrinogen functional/antigenic ratio: >0.7		
	Hypodysfibrinogenemia		AD	UD	PT: P APTT: P TT: P RT: P Fibrinogen activity: <1.5 g/L Fibrinogen antigen: <1.5 g/L Fibrinogen functional/antigenic ratio: < 0.7		
	Dysfibrinogenemia		AD	UD	PT: Usually P APTT: Usually P TT: Usually P RT: Usually P Fibrinogen activity: <1.5 g/L Fibrinogen antigen:< 1.5 g/L Fibrinogen functional/antigenic ratio: < 0.7		

(continued)

Table 11.5 (continued)

Factor deficiency	Subtype	Gene	Inheritance	Incidence	Diagnosis	Therapeutic choice	Clinical manifestations
FII deficiency		*F2* (11p11–q12)	AR	1/2,000,000	PT: P APTT: P TT: N FII activity: D FII: Ag: V[a]	PCC FFP	Hemarthrosis Post-dental extraction bleeding Postoperative bleeding GI bleeding
FV deficiency		*F5* (1q24.2)	AR	1/1,000,000	PT: P APTT: P FV activity: D FV: Ag: V[a]	FFP	Epistaxis Menorrhagia Postoperative bleeding GI bleeding
CFV and FVIII deficiency		*LMAN1* (18q21.3–q22) *MCFD2* (2p21–p16.3)	AR	1/1,000,000	PT: P APTT: P FV activity: D FV: Ag: D FVIII activity: D FVIII: Ag: D	FFP rFVIII	Post-dental extraction bleeding Post-major surgical bleeding Post-circumcision bleeding
FVII deficiency		*F7* (13q34)	AR	1/500,000	PT: P APTT: N FVII activity: D FVII: Ag: V[a]	rFVIIa PCC FFP PdFVII	Menorrhagia Hemarthrosis GI bleeding CNS bleeding
FVIII deficiency		*F8* (Xq28)	AR	1/5000M	PT: N APTT: P FVIII activity: D FVIII: Ag: D	PdFVIII rFVIII EHL FVIII	Hemarthrosis Post-dental extraction bleeding Postoperative bleeding

FIX deficiency	*F9* (Xq27.1)	AR	1/30,000M	PT: N APTT: P FIX activity: D FIX: Ag: D	PdFIX rFIX EHL FIX	Post-dental extraction bleeding Hemarthrosis Hematoma
FX deficiency	*F10* (13q34)	AR	1/1,000,000	PT: P APTT: P RVVT: P FX activity: D FX:Ag: D	PCC PdFX	Menorrhagia Hemarthrosis GI bleeding Hemarthrosis ICH
FXI deficiency	*F11* (4q35.2)	AR	1/1,000,000	PT: N APTT: P FXI activity: D FXI:Ag: V[a]	PdFXI	Postoperative bleeding Menorrhagia Post-dental extraction bleeding
FXIII deficiency	*F13A1* (6p24–p25) *F13B* (1q31–q32.1)	AR	1/2,000,000	PT: N APTT: N CST: abnormal FXIII activity: D FXIII:Ag: V[a]		UCB Impaired wound healing ICH Postoperative bleeding Miscarriage
VKDCFD	*GGCX* (2p12) *VKORC1* (16p11.2)	AR	1/1,000,000	PT: P APTT: P FII activity and Ag: D FVII activity and Ag: D FIX activity and Ag: D FX activity and Ag: D	Vitamin K PCC FFP	ICH UCB Post-trauma/ postoperative hemorrhage Hemarthrosis Gingival/oral bleeding

(continued)

Table 11.5 (continued)

Factor deficiency	Subtype	Gene	Inheritance	Incidence	Diagnosis	Therapeutic choice	Clinical manifestations
VWD	Type 1-VWD	*VWF* (12p13.3)	AD	1/1000	VWF:Ag: D/ABS[b] VWF:GPIb binding: D/ABS VWF:CB: D/ABS FVIII:C: D Multimers: ABS	FFP Cryoprecipitate FVIII/VWF concentrate rVWF	Epistaxis Postoperative bleeding Postpartum bleeding Hemarthrosis CNS bleeding
	Type 2-VWD		AD or AR	UD			
	Type 3-VWD		AR	1/1,000,000			
GT		*ITGA2B* and *ITGB3* (17q21.31-32)	AR	1/1,000,000	PLT count: N PLT morphology: N PT and APTT: N BT/CT (PFA-100/200): P CR: Absent PLT integrin αIIbβ3 expression: UD or D PLT integrin αIIbβ3: < 5% PLT aggregation: ABS	Platelet transfusion rFVII	Epistaxis Menorrhagia Gingival bleeding GI bleeding Hematuria CNS bleeding UCB Hemarthrosis
BSS		*GP1BA* (17p13) *GP1BB* (22q11.21) *GP9* (3q21)	AR	1/1,000,000	PLT count: D PLT morphology: Large or giant platelet PT and APTT: N BT/CT (PFA-100/200): P RIPA: Defective PLT aggregation: Decrease in response to low dose of thrombin Flow cytometry: GP1b-IX-V (CD42a-d)	Platelet transfusion rFVII	Postpartum hemorrhage Ecchymosis Post-dental extraction bleeding Menorrhagia CNS bleeding

GPS	*NBEAL* *GFI1B* *GATA1*	AR		PLT count: D PLT morphology: Macrothrombocytopenia, gray platelet PT and APTT: N BT: P TEM: D α-granules LTA: Defective in response to thrombin and collagen B12 concentration: May be increased	Platelet transfusion	Epistaxis Easy bruising Menorrhagia Splenomegaly Ecchymosis ICH Postoperative bleeding Post-dental extraction bleeding

AD, autosomal dominant; AR, autosomal recessive; M, male; FI, factor I; FII, factor II; FV, factor V; CFV and FVIII, combined factor V and factor VIII; FVII, factor VII; VKDCF, vitamin K dependent coagulation factor; FX, factor X; FXI, factor XI; FXIII, factor XIII; VWD, von Willebrand disease; GT, Glanzmann thrombasthenia; BSS, Bernard-Soulier syndrome; GPS, Gray Platelet syndrome; FFP, fresh frozen plasma; Pd, plasma derived; PCC, prothrombin complex concentrate; EHL, extended half-life; GI, gastrointestinal bleeding; CNS, central nervous system; UCB, umbilical cord bleeding; ICH, intracranial hemorrhage; P, prolonged; N, normal; D, decreased; ABS, absent; V, variable; UD, undetectable; NA, not applicable; PT: prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; RT, reptilase time; BT, bleeding time; PLT, platelet; CT, closure time; CST, clot solubility test; TEM, thromboelastometry; LTA, light transmission aggregometry; ADP, adenosine diphosphate; PFA, platelet function analysis; CR, clot retraction; RVVT, Russell's viper venom time; VWF:CB, von Willebrand Factor collagen binding; Ag, antigen

[a]Usually in type 1 the antigen level is decreased, while in type 2 antigen level is normal

[b]Data were presented for type 3 VWD

Table 11.6 Anesthetic considerations for patients with congenital bleeding disorders

Hemophilia
• Perioperative administration of hemoderivative or recombinant FVIII (for hemophilia A), FIX (for hemophilia B) and FXI (for hemophilia C)
• Preoperative inhibitor screening and assay, if the resumption of plasma factor activity is less than anticipated
• Use recombinant product in patients who generate inhibitor against coagulation factor
• Dosing regimen and duration of coagulation factor should provide coverage adequate up to the postoperative phase
• For the best laboratory and blood bank support, schedule the time of surgery at the start of the week and beginning of the day
• Avoidance of NSAIDs administration
• Use endotracheal tube for mechanical ventilation in patients with active pharyngeal bleeding to avoid airway obstruction
• Avoidance of preoperative mucosal trauma and intramuscular injection of analgesia for post-operative pain management
VWD
• Preoperative administration of DDAVP in VWD type 1 at least 90 min before operation
• Preoperative administration of VWF or FVIII concentrates in VWD type 2 and 3
• Use recombinant product in patients who generated inhibitor against coagulation factor
• During labor epidural anesthesia is not recommended in type 2 or 3 VWD
RBDs
• Replacement of deficient coagulation factor preoperatively by using hemoderivative or recombinant products
• Anesthetic considerations for patients with inherited thrombophilia risk factors
• Preoperative replacement therapy with AT concentrate or FFP in patients with AT III or protein C/S deficiency respectively
• Perioperative anticoagulation
• Consideration of drug clearance in patients with kidney damage when anticoagulated
• Choice of general anesthesia versus regional anesthesia should be individualized per patient and surgery
• Avoidance of N2O-containing general anesthesia in patients with MTHFR deficiency
• Use IVC filter to avoid the risk of pulmonary embolism
• Avoidance of dehydration and minimizing the duration of immobilization
• Use of mechanical compression devices like intermittent pneumatic compression

while they do have a high rate (8–10%) of thromboembolic events. Patients with the disorder are in a hypercoagulable state due to impaired fibrinolysis. Perioperative thromboembolic risk is relatively high in patients with FXII deficiency.

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Chapter 12
Personalized Medicine in Body Fluid Management

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Introduction

The human body consists mainly of water, in which many molecules (electrolytes and proteins) are dissolved.

Water within the human body ranges according to the age: in infants, it's about 75% of body weight, lowering down to approximately 60% in adults and to 45% in elderlies. It is distributed into two main compartments: intracellular space (ICS), which contains nearly 55% of body water, and extracellullar space (ECS), which is further divided into three spaces—the intravascular space (IVS), the interstitial space (ISS) and the transcellular space (TCS). Extracellular space contains approximately 45% of body water (15 L in a normal adult), although it could vary depending on many factors which affects the fluid imbalance, reducing the circulating volume (massive blood loss, severe dehydration) (Brandstrup 2006; Chappell et al. 2008).

Intravascular space contains about 15% of extracellular fluid (ECF), composing the fluid component of blood, plasma. It is separated by the vessel walls in the interstitial space, which is around 45% of ECF. Transcellular space (40% of ECF) is a functional compartment of fluids and electrolytes continually exchanging cells and plasma with ISS. All these compartments, are separated by a semi-permeable membrane made up by a phospholipidic bilayer: water and small solutes can move through this membrane from one compartment to another.

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Properties of Body Fluids

Fluids and electrolytes pass through semi-permeable biological membranes thanks to different forces: hydrostatic, osmotic and oncotic. Particles dissolved in body fluids are responsible for osmolarity and osmolality, the two main colligative properties of solutions, which only depend on the number of particles dissolved in a solution. Osmolarity is the measure of solute concentration, defined as the number of osmoles (Osm) of solute per litre (L) of solution (Osm/L). The osmolarity of a biologic fluid is usually expressed as mOsm/L. Ionic compounds, such as salt, can dissociate in solution into their constituent ions. Van't Hoff factor considers the degree of dissociation of ionic compounds, in an ideal solution it is equal to the number of discrete ions in a formula unit of the substance. For example, a 1 L solution containing 1 mole of NaCl is 2 Osm, because NaCl dissociates completely in sodium and chloride ions (Van't Hoff factor is 2). Non-ionic compounds, such as glucose, do not dissociate in a solution, therefore Van't Hoff factor is 1 and a 1 L solution of 1 mole of glucose is 1 Osm. Osmolality is the measure of solute concentration defined as the number of osmoles (Osm) of solute per Kg of water. While osmolarity expresses the concentration of particles (Osm) per volume of solution, osmolality refers to the mass of solvent.

Plasma osmolality is primarily regulated by Antidiuretic Hormone (ADH), produced by hypothalamus and secreted by posterior pituitary gland in response to any increase of plasma osmolality (closely related to plasma sodium concentration). One of the mechanisms of action of ADH is to increase free water reabsorption by kidney in collecting tubules, thus correcting plasma osmolality.

When two solutions with different osmolarities are separated by a semi-permeable membrane, which allows only water (not solutes) to pass freely through it, water moves from the solution with lower concentration to the one with higher concentration. Osmotic pressure is responsible for this movement of water and depends on electrolytes' concentration of the solution.

Tonicity is a measure of the effective osmotic pressure gradient between two solutions with different osmotic pressure. It depends on the relative concentration of solutes dissolved in solution and determines quantity and direction of movement of water.

Plasma tonicity is 288 ± 5 mOsm/kg H_2O; mainly depends on Na concentration, but Cl, glucose and urea can influence it as well. Plasma tonicity forces water to move in and out of the cell, hence Na concentration affects the relative volume of ICF and ECF.

Infused solution can be isotonic (same tonicity as plasma), hypotonic (lower tonicity than plasma) and hypertonic (higher tonicity than plasma). Hypotonic solutions reduce plasma osmotic pressure, causing water to move from bloodstream to the cell. Hypertonic solutions increase plasma osmotic pressure, causing water to move from the cell to plasma.

Oncotic or colloido-osmotic pressure (π) is a form of osmotic pressure due to proteins, mainly albumin, which cannot cross the semi-permeable membrane, thus

determining water to cross biological membranes from low- to high-protein concentration solutions. Thanks to oncotic pressure blood draws water from ISS into capillaries, contrasting the hydrostatic pressure.

Starling equation describes fluid filtration through capillary membrane:

$$J_v = K_f \left(\left[P_c - P_i \right] - \sigma \left[\pi_c - \pi_i \right] \right)$$

Transendothelial fluid exchange depends on six factors:

- Capillary hydrostatic pressure (P_c);
- Interstitial hydrostatic pressure (P_i);
- Capillary oncotic pressure (π_c);
- Interstitial oncotic pressure (π_i);
- Filtration coefficient (K_f), which depends on surface and permeability of the membrane;
- Reflection coefficient (σ).

Net fluid filtration is proportional to net driving force. For convention, outward force is positive, inward force is negative, so when it is positive, fluid leaves bloodstream moving to the interstitial space, when it is negative, fluid enters the capillary (absorption).

Perioperative fluid management is a central part of any surgical procedure and it starts before the operation, since the patient should be allowed and, sometimes, encouraged to drink clear fluids such as water, fruit juice without pulp, carbonated beverages, carbohydrate-rich nutritional drinks, clear tea and black coffee (Smith et al. 2011; 2017).

A meta-analysis of randomized trials reports a lower risk of aspiration (gastric volume less than 25 mL and pH greater than 2.5) when clear liquids are given 2–4 h before a procedure compared with fasting overnight. After an 8-h "fast," roughly 500–1250 mL of fluid is added naturally to the stomach (Nordgren 1963). Allowing unrestricted access to clear fluids (preferably containing carbohydrates) up to 2 h before surgery reduces the acidity of gastric contents which is likely to improve patient comfort and safety.

Fluid Losses

Loss of fluid and electrolytes occurs continuously, due to many factors. Insensible perspiration is the only loss of pure water in the body, through the skin and the respiratory system. During surgery, the amount of water loss increases, due to perspiration through the surgical wound and exposed internal organs. This is particularly true in major abdominal surgery (Lamke et al. 1977). Diuresis is another source of fluid loss, depending on many factors including blood pressure, fluid intake, stress response, surgical trauma and anesthesia.

Blood loss is variable case-by-case, but severe bleeding may occur during surgery, due to either vascular damage (e.g. arterial bleeding) or to non-vascular sources of hemostatic perioperative bleeding (bleeding disorder, hemodilution or hemostatic factor consumption, fibrinogenolytic and inflammatory pathways, and hypothermia) (Ghadimi et al. 2016).

Physiological responses to acute blood loss are both activation of the sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS), which accordingly enhance ADH levels. Such responses lead to a fluid shift from the extravascular space to the intravascular one, resulting in plasma volume restoration and decrease in colloid-osmotic pressure. After a 30% blood loss, return to a normal plasma protein concentration (80% COP) occurs within 24 h. The body replaces a blood loss $\leq$ 15% (about 750 mL) in about 24 h, without administering any intravenous fluid (Lundvall and Länne 1989).

Crystalloids vs. Colloids

Starting from 1913 (Nadler et al. 1962), a wide amount of literature about fluids was published. Different solutions are commercially available, but debate remains concerning the characteristics of the ideal fluid.

Crystalloids

Crystalloid solutions are composed by low-molecular weight salt, dissolved in water that pass freely from the plasma to the interstitial space and vice versa (McIlroy and Kharasch 2003).

There are four generations of crystalloids available on the market, classified into hypertonic, isotonic and hypotonic depending on their tonicity:

- Normal Saline Solution: contain only sodium and chloride at 0.9% and high concentration (154 mmol/L). It is a hypertonic fluid (osmolality 308 mOsm/kg).
- Ringer Lactat and Ringer Acetate: compared to saline solution, they contain less sodium (130 mmol/L) and less chloride (112 mmol/L). Moreover, they contain potassium, calcium, magnesium and metabolizable ions: lactate (Ringer Lactate) and acetate (Ringer Acetate) (Agrò 2013; Agrò et al. 2018a, b)
- STEROFUNDIN (ISO): it is the latest-generation of Crystalloids and its ionic composition is very close to the one of plasma: a lower chloride content together with both acetate and malate. As a result, it is an isotonic, balanced and plasma-adapted solution, which reduces the risk of chloride excess and dilutional acidosis, with a decreased influence on lactate monitoring, lactic acidosis and base excess (Agrò 2013; Agrò et al. 2018a, b)

Olson et al. found that only 20% of administrated crystalloids are distributed within the vascular space, and of these, 30% remains there for 30 min (Olsson et al. 2004). The 80% of the infused fluids is distributed in the EVS. Thus, crystalloids can be used for short-term volume expansion, but they do not actually help in restoring fluid balance and blood pressure in case of massive or rapid loss of fluids.

In this case, massive and repeated infusions of crystalloids are required, which, on the other hand, are likely to cause interstitial edema and electrolyte imbalance.

Therefore, the use of hypertonic crystalloid solutions (HCS), containing high concentrations of sodium (3–7.5%), was initially proposed. HCS appears to have direct cardiovascular effects, improving inotropism, also leading to vasodilation and reduction of venous compliance. If administered together with colloids it has shown prolonged effectiveness in volume expansion (Coppola et al. 2014).

Wade et al. (1997) and Bunn et al. (2004) hypothesized in their meta-analyses that the combined use of HCS and dextran would be superior to isotonic fluid resuscitation. HCS causes a rapid shift of water from EVS, to IVS, without a reduction in COP.

The initial enthusiasm for the HCS in patient with refractory hypovolemic shock states has gradually diminished because of side effect danger. Among them, the most significant is albumin dilution, which could also cause tissue edema. These effects cause a reduction in colloid oncotic pressure (COP) that, in critically ill patients, is associated with a mortality rate of 50% (Morissette et al. 1975; Rackow et al. 1977).

Excessive use of crystalloids results in the development of "compartments syndrome" as well. The hemodilution also causes a decreased concentration of antithrombin III and a hypercoagulability state (Ruttmann et al. 2002; Agrò 2013; Agrò et al. 2018a, b).

Colloids

Colloids are high molecular weight molecules that do not freely pass through membranes as they are not completely soluble in water. Colloids determine the oncotic pressure and, in proportional measure, the initial volume increase in the intravascular space. The high molecular weight (MW) also determines the volumetric expansion (Mitra and Khandelwal 2009).

In another study, it was found that an isotonic colloid is distributed only within the IVS, therefore a 100% plasma volume expansion results from the clinical use of this fluid (McIlroy and Kharasch 2003). Many colloids are currently available, differing in their physicochemical properties, pharmacokinetics, clinical effects and safety.

Natural Colloids: Human Albumin (HA)

HA is the main plasma protein, responsible for 80% of normal oncotic pressure. It is made up of 585 amino acids, with a molecular mass of 69,000. For many years it has been considered the gold standard treatment for acute hypovolemia, especially following trauma, surgical hemorrhage and cardiac surgery. However, HA is not exclusively retained in the IVS; rather, about 10% of HA leaves the IVS within 2 h and moves into interstitial space, with the risk of aggravating pre-existing interstitial edema or hypoalbuminemia. In fact, HA potentially causes or worsens pulmonary edema, especially in critically patients where a rapid volume replacement may cause cardiac failure. HA also may impact coagulation and hemostasis by enhancing antithrombin III activity and inhibiting platelet function (Nadler et al. 1962; Jøorgensen and Stoffersen 1979; Rozich and Paul 1989; Roberts and Bratton 1998; Randolph et al. 2002; McIlroy and Kharasch 2003; Ertl et al. 2007; Feldschuh and Katz 2007; Goepfert et al. 2007; Mutoh et al. 2007; Bunn et al. 2008; Mitra and Khandelwal 2009; Bunn et al. 2011; Smith et al. 2011; Bunn and Trivedi 2012; Agrò 2013; Padashi et al. 2016; Agrò et al. 2018a, b; Sezari et al. 2018).

Currently, HA is strictly indicated in acute condition requiring plasma expansion and in chronic conditions characterized by low albumin plasma levels (Vincent et al. 2003):

- > 5 L or > 5 g/L of albumin in ascites fluids after paracentesis
- Therapeutic plasmapheresis: plasma exchange > 20 mL/kg
- Spontaneous bacterial peritonitis in cirrhosis.

Synthetic Colloids

According to concentration, initial volume effect and duration of the volume effect they are further classified in dextrans, gelatins and hydroxyethyl starches.

Dextrans

Dextrans are glucose polymers of different size, mainly used in USA, which can lead a 100–150% volume increase of the IVS. Only a small fraction transiently passes into ISS (Agrò 2013; Agrò et al. 2018a, b). Their main clinical use is the maintenance of hemodynamic stability in different types of shock, improving both tissue perfusion and microcirculation. However, they can have different side effects. In fact, they have the greatest risk of anaphylactoid reaction compared to other colloids, can cause renal failure especially in elderly and dehydrated patients or with pre-existing renal dysfunction. Finally, dextrans may cause bleeding disorders, as they can alter platelet function, reduce factor VIII and increase fibrinolysis (Feldschuh and Enson 1977; Haeberle et al. 2006; Feldschuh and Katz 2007).

Gelatins

Gelatins are polydispersed peptides derived from bovine collages (6 L), available in most European and Asian countries. Gelatins' MW is about 30–35,000 and they are based on unbalanced, hypotonic solutions (Agrò 2013; Agrò et al. 2018a, b).

Particularly, there are three types of gelatins currently available:

- Cross-linked or oxypolygelatins, generally containing Na+ 145, K+ 5.1, Ca++ 6.25 and Cl– 145 mmol/L
- Succinylated or modified fluid gelatins, containing Na+ 154, K+ 0.4, Ca++ 0.4 and Cl– 120 mmol/L
- Urea cross-linked gelatins

Gelatins have a shorter duration effect than any other colloid, with a similar IVS volume- expanding power between them and a half-life of about 2.5 h (12). Therefore, they are associated with a lower risk of kidney injury compared to starch solution and there are no dose limitations, in contrast to other colloids. On the other hand, potential adverse effects are:

– Anaphylactic reaction
– Hemodynamic impairment, particularly after massive paracentesis in ascitic patients, due to increased plasma aldosterone and renin activity
– Coagulation disorders, which however do not have great clinical significance (Kato et al. 2001; Haeberle et al. 2006; Levi and Jonge 2007; Ertmer et al. 2009; Mitra and Khandelwal 2009; Hartog et al. 2011).

Hydroxyethyl Starches (HES)

HES are modified natural polysaccharides derived from maize or potatoes amylopectin, with hydroxyethyl groups at the C2, C3 and C6 carbon position of anhydroglucose residues instead of hydroxyl groups, which confers resistance to degradation by plasma amylases and greater solubility.

HES are described by a series of numeric parameters that reflect their pharmacokinetics (Barron et al. 2004; Agrò 2013; Perel et al. 2013; Agrò et al. 2018a, b)

– The first number represents the solution concentration that influence the volume expansion power (3, 6, 10%). HES at 6% concentration is iso-oncotic and have a 100% volume-expanding power; HES at 10% concentration are hyper-oncotic and have a volume- expanding power > 100%
– The second one relates to the mean MW (lower MW: 70 kDa, medium MW: 130–270 kDa, high MW: >450 kDa). MW determines the duration of volume-expansion, as lower MW is associated with faster elimination
– The third number is the molar substitution rate (MRS): low MRS is 0.4–0.5; high MRS is 0.62–0.7. MRS is the molar ratio of the total number of hydroxyethyl groups to the total number of glucose units. It is inversely proportional to the rate

of degradation, while it is directly proportional to the duration of the volume effect and to the incidence of adverse effects

– The fourth is the C2/C6 ratio: it represents the quotient of the total number of hydroxyethyl groups on carbon atom 2 and the total number of hydroxyethyl groups on C6. The higher the ratio, the more groups will be present in C2 and the greater will be the resistance to plasma amylase and, therefore, the volume effect

HES solutions have a high hemodilution power, which leads to a reduction in vascular resistance and an increase in venous return. For this reason they have been widely used in hypovolemic patients, even in critically conditions, thanks to the low rate of infection related to HES administration.

Furthermore, HES administration is potentially associated with risks and side effects. HES can cause a reduction in von Willebrand factor, fibrinogen levels and thrombin generation with a severe increase in the bleeding risk. Another side effects of HES is impaired platelet function. However, there is a wide debate about the clinical impact on coagulation with the use of HES with a medium MW and a low MRS (Agrò 2013; Agrò et al. 2018a, b).

In cardiac and orthopedic surgery patients new-generations HES increase von Willebrand factor levels, resulting in a reduction of bleeding risk and transfusion need. Similar results were reported for minor elective surgery. Administration of HES increases the risk of kidney failure, especially in patient treated with high MW and high MRS HES and in elderly patient with previous renal dysfunction or other comorbidities. Kidney damage appears to be related to tubular obstruction caused by hyper-oncotic urine. Adequate hydration with crystalloids could prevent this damage. However, recent literature suggests that the latest generation of HES is the best colloid solution in kidney protection from oncotic damage, although the influence of HES on kidney function remains controversial. A decreased incidence of anaphylaxis with HES is found compared to other colloids. Prolonged administration of large amount of HES may cause itching. Itching is due to storage of the material in small peripheral nerves and appears weeks or even months after HES administration. Finally, since HES are similar to glycogen, they have potential to interfere with blood glucose levels (Kozek-Langenecker et al. 2008; Liu et al. 2009; Lindroos et al. 2010; Agrò 2013; Agrò et al. 2018a, b).

Goal-Directed Fluid Therapy

The administration of fluids to obtain better oxygenation and tissue perfusion is an elaborated strategy called Goal-Directed Therapy (GTD). GTD allow doctors to dose fluids and various drugs (e.g. inotropic, vasoactive, etc.) and administer them at the right time, only to those patients who need them, thanks to hemodynamic monitoring. GDT permits a personalized fluid therapy, based on the need of every single patient. Fluid responders will generally demonstrate an increase in their SV by >10–15% after a fluid challenge; the definition of fluid challenge typically refers

to a fluid volume administered over a short period of time (example a bolus of 500 mL or more in 10 min or less). It is important to understand that being a fluid responder is not equal to being hypovolemic (Miller et al. 2015; Yamada et al. 2018; Kendrick et al. 2019).

Physiology

The principle behind GDT is to optimize peripheral oxygen delivery without fluid overload. Oxygenation and tissue perfusion are both vitals for elective surgery and critical ill patients. DO2 (oxygen delivery) must be assured in adequate quantity every minute by respiratory and cardiovascular system (Miller et al. 2015; Kendrick et al. 2019).

$$\mathrm{DO2}\left(\mathrm{mL/min}\right)=\mathrm{CO}\left(\text{Cardiac Output}\right)\times\mathrm{CaO2}\left(\text{arterial oxygen content}\right)$$

$$\mathrm{DO2}=900-1000\,\mathrm{mL/min}\,\text{or}\,500-600\,\mathrm{mL/min/m^2}\,\text{under physiologically conditions.}$$

CO and CaO2 are determined by various factors; CO depends on heart rate (HR) and stroke volume (SV), CaO2 depends on the amount of Hb in g/dL, the number of mL of oxygen carried by every g of Hb (1.34), the O2 saturation of arterial blood and the O2 partial pressure of arterial blood. Considering all these factors, the previous equation can be rewritten as follow:

$$\mathrm{DO2}\left(\mathrm{mL/min}\right)=\left(\mathrm{HR}\times\mathrm{SV}\right)\times\left[\left(1.34\times\mathrm{Hb}\times\mathrm{SaO2}\right)+\left(0.003\times\mathrm{paO2}\right)\right]$$

where 0.003 is the solubility coefficient of O2 in blood.

SV can be modified using vasoactive, inotropic drugs or fluid administration; Hb by blood transfusion; SaO2 and paO2 by mechanical ventilation.

VO2 is the oxygen consumed by tissue per minute (mL/min). VO2 is usually increased during stressful situation, like surgery and critical conditions.

$$\mathrm{VO2}\left(\mathrm{mL/min}\right)=\mathrm{CO}\times\left(\mathrm{CaO2}-\mathrm{CvO2}\right)$$

where CvO2 is venous O2 content. It can be rewritten as follow:

$$\mathrm{VO2}\left(\mathrm{mL/min}\right)=\left(\mathrm{FC}\times\mathrm{SV}\right)\times\begin{bmatrix}\left(1.34\times\mathrm{Hb}\times\mathrm{SaO2}\right)+\left(0.003\times\mathrm{paO2}\right)\\-\left(1.34\times\mathrm{Hb}\times\mathrm{SvO2}\right)+\left(0.003\times\mathrm{pvO2}\right)\end{bmatrix}$$

where SvO2 is the O2 saturation of venous blood; PvO2 is the partial O2 pressure of venous blood. Normally, VO2 is around 200–300 mL/min; it could increase

for 4–6 times under stress conditions. The fraction of DO2 released to the peripheral tissues per minute is called O2 extraction. It can be expressed as follow:

$$O2ER = VO2 / DO2.$$

Normally, O2ER is 0.25, but it could increase. Below a critical value of DO2, O2ER can not increase anymore, and the flow become a VO2 determiner; tissue hypoxia could appear and anaerobic metabolism starts. This process can cause a discrepancy between ATP request and production. cAMP and cGMP decrease cause an activation of the endothelium and the release of pro-inflammatory cytokines that lead to capillary leak syndrome; the endothelial barrier falls, exposing the blood to leukocyte adhesion molecules and pro-coagulant factors. The leukocytes activation lead to a systemic inflammation, organ hypoperfusion and failure. It is clear that Hypoxia must be early detected and prevented when possible; this can be done with a correct approach to fluid therapy (GDT). A lack in the compensatory system of VO2 increasing due to vascular comorbidities, can lead in some patients to a higher probability of a fall of DO2 during stress conditions; a GTD approach can be crucial in these patients (Lees et al. 2009; Kendrick et al. 2019).

Hemodynamic Variables

In the GDT approach, it is crucial to predict the fluid responsiveness. The target is to identify the responders, patients who would benefit from high fluid administration in terms of DO2 and hemodynamic parameters, giving fluid boluses only to the ones who need them. To identify the responders, it is important to define hemodynamic variables that can be split into static and dynamic. A static variable for example can be the cardiac index obtained during a single thermodilution, thanks to the Swan-Ganz catheter. It indicates a hemodynamic status at a specific time. On the other hand, dynamic variables are hemodynamic changes due to a periodic pre-load variation; they are the best way to understand if a patient is a responder or not (Lees et al. 2009; Miller et al. 2015; Kendrick et al. 2019).

The CVP measurement is still widely used to guide intravascular volume therapy. Some recent studies, however, have shown that CVP is not a good pre-load indicator and is not effective in predict fluid responsiveness. PPV (pulse pressure variation) has also been recently considered; it defines the difference between diastolic and systolic pressure at different heart beats. It is defined by variation of intrathoracic pressure due to mechanical ventilation. This variation cause a change in pre-load volume; it has been demonstrated that PPV can be used to guide volume therapy (Drage and Boyd 2007; Lopes et al. 2007; Abbas and Hill 2008; Cavallaro et al. 2008; Malbouisson et al. 2017).

Other useful parameters are SVV (stroke volume variation) and CI; they can be obtained by the analysis of the pulse wave. To calibrate the pulse wave analysis, intermittent transpulmonary thermodilution can be used, enhancing the trustworthiness of CI measurements. It can also be used to measure ELVW (extravascular lung water), SVV (stroke volume variation), GEDV (global end diastolic volume); these three are called "the golden triangle", and can be used together for GDT assessment.

$$\mathrm{SSV} = \left(\mathrm{SV\,max} - \mathrm{SV\,min}\right) / \mathrm{SV\,mean}$$

SVV is simile to PPV but more precise; it is based on cyclic changes in SV caused by intrathoracic pressure oscillation during mechanical ventilation. With other variables, it can indicate the real-moment position on the Frank-Starling curve. The intrathoracic pressure variation cases changes in pre-load and SVV (SVV > 13%) when the heart operate on the ascending tract on the Frank-Starling curve; this indicates a good pre-load reserve and CI improvement after the administration of fluid, identifying the fluid responders. Very little variation of CI after fluid loading is noticed at the Frank-Starling curve plateau, with small SVV change (SVV < 13%) after intrathoracic pressure change, suggesting a small pre-load reserve; inotropes may be useful in these patients (Lees et al. 2009; Reuter et al. 2010; Agrò 2013; Agrò et al. 2018b).

SSV has some limitations that may exclude his use:

- Arrhythmias
- Right ventricular failure
- Spontaneous breathing
- Ratio heart rate/respiratory rate < 3.6
- Low tidal volume (<8 mL/kg)

GEDV is a good indicator of pre-load; it is a static variable that is unable to determinate the patient fluid responsiveness. EVLW can be used in case of acute lung injury or left ventricular failure. It is a predictor of patient's survival. Its use in GDT speeds up the treatment of lung edema, caused by increased vascular permeability or hydrostatic pressure (Drage and Boyd 2007; Goepfert et al. 2007; Lopes et al. 2007; Mutoh et al. 2007; Kapoor et al. 2008; Lees et al. 2009; Malbouisson et al. 2017; Kendrick et al. 2019).

A positive post-operative outcome could be seen if a GDT approach (GEDV > 800 mL/m^2; EVLW = 10–12 mL/kg) is used in cardiac surgery patients. In order to prevent secondary brain injury, CI was maximized using GEDV and EVLW, in patients with subarachnoid hemorrhage; during GDT protocol no congestive heart failure was observed (Chytra et al. 2007; Drage and Boyd 2007; Goepfert et al. 2007; Abbas and Hill 2008).

Monitoring System

Due to the risk associated with excessive fluid administration, it is important to predict whether a patient is a fluid responder without actually giving fluid. Checking the response to a 30° Trendelenburg position is an option to do that (Miller et al. 2015; Kendrick et al. 2019).

The hemodynamic monitoring is fundamental in GDT; obviously, the perfect system of monitoring should be non-invasive, simple, safe for the patient, precise and immediate, but unfortunately an ideal system has not been found yet. Recently, anyway, a lot of systems have been proposed; all of them have to be compared with the gold standard, the Pulmonary Artery Catheter (PAC) or Swan Ganz, which is not recommended in the routine operative settings, even if GDT is used. It is invasive, it exposes the patient to a not justified risk and requires high skills and experience for its placement; its fame in clinics practice has fallen, especially in the last years, thanks to the advent of less invasive techniques (Lees et al. 2009; Agrò 2013; Agrò et al. 2018b).

The new technologies permit the measurement of more precise filling volume values related to pre-load and fluid responsiveness; for example, arterial pressure wave form analysis and Doppler technologies are less invasive and permit an accurate measurement of cardiac output or SV.

ED (Esophageal Doppler) can be used for the measurement of blood flow time (FTc) in the descending aorta, which corresponds to the SV. FTc is normally 330–360 ms. If FTc is lower, hypovolemia should be suspected. This technique requires less training and does not require calibration; on the other hand, like any ecographic technique, it is operator-dependent and is difficult to use on an awake and not compliant patient. The use of ED has shown to improve patients outcomes during GDT, reducing blood lactate levels, infections, duration of the ICU and hospital stay in trauma patients and reducing complications, requirement of inotropes, ICU admissions and hospital stay in patients undergoing major abdominal surgery (Chytra et al. 2007; Drage and Boyd 2007; Mutoh et al. 2007).

PiCCO (Pulsion Medical System) and EV1000 System: they provide parameters that improve GDT, combining pulse wave analysis and trans-pulmonary thermodilution. They require invasive arterial cannulation and CVC, but they still are less invasive than PAC.

PiCCO analyzes thermodilution curves to find GEDV and EVLW, while EV1000 calculate GEDV thanks to the maximum gradient of the thermodilution curve ascent and descent. The recent findings demonstrate that the two devices are comparable. PiCCO PLUS (an evolution of PiCCO) evaluation of SVV can precisely indicate fluid responders among patients (Drage and Boyd 2007; Goepfert et al. 2007; Lopes et al. 2007; Mutoh et al. 2007; Cavallaro et al. 2008; Lees et al. 2009; Reuter et al. 2010).

FloTrac/Vigileo system: it performs the wave analysis with Langewouters' algorithm and does not required thermodilution, so it can be used with a normal arterial line and nothing else, connected to the FloTrac sensor. GDT protocol through

FloTrac/Vigileo has demonstrated hospital stay and incidence of complications reduction in high risk patients undergoing major abdominal surgery. The Vigileo limits involve the fact that the analysis of the wave pressure and SSV values are valid only in patients who are mechanically ventilated (Benes et al. 2010; Reuter et al. 2010).

Nefxin HD monitor: is a new non-invasive monitor that measure continuous CO by an inflatable finger cuff. It continuously measures finger blood pressure and converts it into the blood pressure wave of the brachial artery. It can be used in awake and not mechanically ventilated patients.

Conclusion

Decision regarding fluid therapy are among the most challenging and important tasks that a clinician face every day. Maintenance of intravascular euvolemia throughout the perioperative period is ideal. The main hemodynamic goal in critically ill patients is an optimization of administration of fluids by assessing fluid responsiveness. Load intravenous fluid is required in patients with reduced circulating volume and fluid responders. It seems more rational to give fluid when hypovolemia occurs, and not before it, because the volume effects is more sensitive. It has been demonstrated that GDT is an effective strategy for fluid administration, based on hemodynamic evaluation of the patient.

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Chapter 13
Personalized Medicine and Perioperative Stress Response Modification

Soudeh Tabashi

Introduction

The stress response is "the nonspecific response of the body to any demand upon it" which first of all described by Hans Selye (Goldstein and Kopin 2007). Anesthesia, surgery and trauma to tissues of the body cause imbalance in physiologic status and activate body's response to stress. These chemical mediators that act as stress response, make the organism to react successfully in danger situations. Cardiac output and respiratory capacity increase, glucose level elevate due to catecholamine secretion and finally all the organisms will be ready to defense of body in stress conditions. But it does not always have positive effect. Sometimes these increasing in stress responses make trouble because they can cause hemodynamic instability and high catabolic state and are thought to correlate to morbidity and even mortality in many organs by increasing their task during defensing body especially when we have malfunction in some of them. Reducing stress factors can actually improve surgical outcome.

So, during a surgical procedure we have too many stress factors that can cause too many stress responses in body. These stress response can cause complications (Fig. 13.1). For example, hypercoagulable state such as deep vein thrombosis, vascular graft failure and myocardial ischemia can be enhanced by stress factors. They also can enhance postoperative immunosuppression, poor wound healing due to postoperative hyperglycemia, delay return of postoperative gastrointestinal motility and sodium and water retention. Stress factors can inhibit phrenic nerve activity and cause postoperative pulmonary complications. These complications can increase postoperative morbidity and mortality. Cortisol level increase after a major trauma up to twofold or threefold.

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Fig. 13.1 The list of stress factors, stress responses and complications

Studies show that the response to stress can be different inter individual. Cortisol response to trauma increases with age and is more in females (Otte et al. 2005).

Surgery is a painful and stressful procedure. After tissue injury and increase of inflammatory mediators, they stimulate peripheral nerve fibers and produce the perception of pain. Now both pain and inflammatory mediators can cause a big amount

of response in body due to increasing sympathetic activity and stimulate corticotropin releasing hormone brain center. One of the traditional method to decrease these complications is control postoperative pain especially with preemptive analgesia method (Miller 2015).

We have to anesthetize many pregnant women, infants and very young children due to variable procedures or even imaging. In a developing brains including fetus and children younger than 2 years old central nervous system is a sensitive organ in exposure to anesthetic drugs. Neurotoxicity is a major concern among postoperative complications.

Traditional Approach

Preoperative Period

Increasing the stress responses during a surgery start preoperatively. First of all, fasting for at least 8 h before surgery cause increases the level of cortisol and catabolism due to hypoglycemic state. This response can be more severe in children and when the operation is not done early in the morning. Solving this problem is not so complicated. Allowing the patients to use carbohydrates till 2–3 h before surgery or to use chewing gum and candies during NPO time can be beneficial.

Many patients are stressful just before elective surgeries and it can activate hypothalamus pituitary axis and sympathetic response. Pharmacologic premedication therapy with opioids, antihistamines, anticholinergic agent, benzodiazepine and melatonin can reduce anxiety as well as nonpharmacologic methods like music, video glasses, and smartphone applications. But they can be more effective if are used in combination (Yousaf et al. 2010; Wang et al. 2002).

Control stress response in preoperative period is very important because even low level of these factors in body can exaggerate the effect of what will release during main surgery.

Intraoperative Period

Does the type of anesthetic drugs that we choose during surgery affect catecholamine release? The answer is yes it can. Most of the hypnotic drugs include volatile anesthetics and IV drugs cannot suppress stress response but there are evidences that propofol with high allowed level can inhibit catecholamine secretion during intubation. In studies it could decrease the level of antioxidants catalase (CAT) and glutathione peroxidase (GPX) more than isoflurane when they had been used as maintenance of anesthesia (Nashibi et al. 2019).

Preoperative use of α2 adrenergic agonists, clonidine and dexmedetomidine can blunt hemodynamic response by reducing norepinephrine release.

Opioids can suppress stress response. Among opioids, combination of alfentanil and propofol could reduce IL-6 level. The main mechanism that can explain this effect is attaching alfentanil to monocyte receptor and cause decreasing release of IL-6 by reducing cAMP in these cells. However, attenuation of IL-6 by other kinds of opioids are controversial (Goldstein and Kopin 2007). Is there any other way to stimulate monocyte receptor? Do interindividual variability in these receptors can explain the reason of differences in research results? We will discuss about it later in this chapter.

Regional anesthesia can cause less inflammatory response than general anesthesia. Evidences show that combined regional and neuraxial block can decreased stress response more than general anesthesia alone. The main mechanism is blocking sympathetic response and in more low surgical site the block work better and difference is more prominent. Epidural anesthesia never can reduce IL-6 secretion because the level of this mediator depends on ACTH and hypothalamus pituitary axis not sympathetic chain. The drugs that is used in neuraxial block can also influence the suppression of stress. Using bupivacaine can be more effective than lidocaine and even intrathecal opioids.

Another intraoperative factor that can be controlled easily is hypothermia, normothermia during surgery can reduce stress response.

Postoperative Period

Patient can have high level of catecholamine response after emergence even with usage of all treatments above just because of postoperative pain and awareness. 12 h postoperative sedation with propofol could just delay stress response not solve the problem. But in trials show that continues postoperative analgesia with epidural catheter can reduce stress response. Maybe just because the main reason of this response is postoperative pain and control it but non-opioid approaches as much as possible to decrease ileus as a complication of opioids and of course a stress factor too.

There are some non-anesthetic approaches to control stress response, using β blockers and preoperative corticosteroids are examples of attempting to attenuate stress response.

Stress Response: Personalized Anesthesia and Perioperative Medicine Approach

The goal of medical science in all of its history have (has) been to understand any details of underlying cause of diseases to treat or predict them better. In the last years, precision medicine has improved to define individual genetics and

environmental variations to treat or predict individual diseases. It can make us to approach our patients more individually. Each human being has unique store of genes, unique disease susceptibility, unique drug metabolism and of course unique method for treatment. As patients response differently to anesthetic drugs, anesthesia has become one of the specialties that challenges with interindividual difference as a routine practice. And it could be the start point of the concept of precision medicine when could solve manifestations like malignant hyperthermia following exposure to volatiles or porphyria exacerbation after sodium thiopental administration (Sezari and Dabbagh 2019).

Relationship between genotype and phenotype is not as simple as Mendelian genetics had described. Many features cannot be related to a single allele. And if you could solve the genetic problems there are more ways to reach the final phenotype. So precision medicine analyzes individual features in a number of newly emerged approaches, these 4 categories are the most commonly known ones: Genomics (genes), epigenetics (modification of gene), Proteomics (proteins) and Metabolomics (metabolites); a more detailed discussion on these topics are provided in Chapter 2.

Genomics

Genomics is a branch of molecular biology that describes all person genes and it is exactly about the structure and mapping of our cell DNA. Understanding the underlying genetic structures and their variations can help us to evaluate the amount of drug in variable situations in accordance with patient's need. To better understanding here we describe relationships between few genes and their effect in clinical practice.

As described previously one of the most important stress factors that can cause a wild variety of acute and chronic stress response in perioperative period is pain. There are many options for controlling post-operative pain including non-pharmacologic methods, systemic drugs and regional analgesic techniques. Opioid are one of the basic drugs that can modulate stress response and commonly used in pain treatment. A balance between the analgesic effect of all modalities and their complications is one of our issues in controlling pain. Misuse of opioids is a serious public health and economic problem. Some patients are more prone to addiction than the others. Overdose symptoms are prominent in some individuals. Current studies in personalized medicine shows that administration of equal dose of opioids to patients in somehow equal clinical conditions can cause different response and complications which related to the genome of them.

Several genes are involved in opioids metabolism such as CYP2D6, CYP3A4, CYP3A5, UGT2B7, ABCB1, ABCC3, SLC22A1, OPRM1, COMT, KCNJ6. Our knowledge about their structures can help us to predict what would happen to every patient in exposure to a specific drug and can be useful for clinical practice in the future (Kaye et al. 2019).

Codeine is a weak opioid that is usually prescribed for chronic pain or postoperative pain especially in children. About 5–10% of total administered codeine is converted to active metabolite morphine after O-demethylation by CYP2D6, that cause the main analgesic effect of the drug (Vree and Verwey-van Wissen 1992). Variability in analgesic effect of codeine make investigators to think about polymorphisms of main metabolizer enzyme, CYP2D6. There are more than 100 polymorphisms that categorized to four groups, ultra-rapid metabolizer (UM) that include alleles with higher than normal function, extensive metabolizer (EM), intermediate metabolizer (IM) and poor metabolizer (PM) that include alleles with no enzyme function (Crews et al. 2014). The function of CYP2D6 is dependent on which and how many alleles are activated. Everybody who is carrying a multiple copy of functional CYP2D6 alleles can have ultra-rapid phenotype of this enzyme which cause more concentration of morphine than the others. In these individuals when one usual dose of codeine is injected CYP2D6 can produce more concentration of morphine as an active metabolite which can cause more pain control and of course more complications. In 2009 a fatality was reported after administration of a standard dose of codeine to a 2 years old baby 2 days after elective tonsillectomy with a history of night snoring. In biopsy there was much concentration of morphine and low concentration of codeine in blood than was expected. In his genotype there was more copy of functional alleles for CYP2D6 (Ciszkowski et al. 2009). It isn't the only death report after codeine administration in children. A review by FDA showed 24 deaths that reported after codeine or codeine containing products especially in children (FDA 2015). And also we have reports that patients with chronic low back pain had resistance to treatment if they had PM alleles of CYP2D6 (Dagostino et al. 2018). For these patients we can use alternative drugs to control postoperative pain that their metabolism is independent of CYP2D6 such as non-opioid drug, tramadol, tapentadol, oxycodone, oral morphine or regional blocks (Zhou 2009; Chidambaran et al. 2017a). This story can repeat about every drug which is metabolized by CYP2D6 include some antidepressants, antipsychotics, antiarrhythmics, antiemetics and beta-adrenoceptor antagonists (beta-blockers).

About the alleles that code CYP2B6 heterozygosity and homozygosity can affect the function of this enzyme which metabolize methadone (Kharasch et al. 2015). Cumulative effect of methadone can increase mortality. And studies show that ABCC3 variant has significant association with respiratory depression after morphine administration in children undergoing tonsillectomy and prolong their postoperative anesthetic care unit stay (Chidambaran et al. 2017b).

Another genome that seems to be effective in opioid response is PXR which can code a p-glycoprotein called ABCB1. This glycoprotein tightens blood brain barrier and decrease the efficacy of drug's CNS efficacy. Patients who carry a variant allele of PXR A7635G need lower dose of sufentanil compare to wild type homozygote in control of post-operative pain (Hronova et al. 2016).

There is a Multi Drug Resistance (MDR) gene that encodes a transmembrane p-glycoprotein in brain which is responsible for transporting certain drugs out of the brain including anesthetic drugs. MDR gene polymorphisms were detected in laboratory and now we know that any types of MDR gene can make different kinds of

p-glycoprotein which some of them are more potent for transporting drugs in brain and some are less. And what does this phenomenon show us in clinical practice? Children undergoing tonsillectomy were administered same dose of propofol and remifentanil and they showed different duration of anesthesia, different hemodynamic response and emergence when they categorized by their MDR genome (Zhang et al. 2018). This is one of the explanation of personalized medicine in genomic field to answer an important question in clinical practice: why patients with same physical condition and same history in same situation can show different responses to same drugs in the same doses?

One of the oldest manifestation of genomics in personalized medicine and its usage in anesthetist practice is Malignant Hyperthermia. MH is the most well-known drug reaction in anesthesia. It was discovered in early 1960s. It takes about 10 years that investigators found there is an inherited feature which cause MH symptoms. 20 years later in about 1990 mutation in Ryanodine receptor was discovered as the main reason of MH (Kaye et al. 2018). The underlying genetic etiology of MH is not only related to RYR. Many patients with RYR1 mutation don't experience MH following halothane exposure and many show symptoms without mutation in RYR1. Studies show there is a gene called calcium voltage-gated channel subunit alpha1 S *(CACNA1S) that* at least six different mutations of this *gene* are need for malignant hyperthermia syndrome (Beam et al. 2016). Beside RYR1 and *CACNA1S other genes are found that could increase the risk of MHS like* Sarcoplasmic/endoplasmic reticulum calcium ATPase 1 (SERCA1), SRC homology 3 (SH3) and cysteine-rich domain 3 (STAC3) (Beam et al. 2016; Horstick et al. 2013).

It shows that how can preoperative genetic evaluation and personalized medicine help us to prevent many questionable perioperative deaths. But the important issue is to make connection between what happen in laboratories and what we need in clinical practice.

Epigenetics

Epigenetics mean the changes in genome that not involve the exact nucleic acid. In fact, it relates to some mechanisms in gene expression other than nucleotides that exist in deoxyribonucleic acid (DNA) such as deoxyribonucleic acid (DNA) methylation, histone modifications and microribonucleic acids (miRNAs).

DNA methylation is methylation of cytosine residues by DNA methyltransferases and cause long term gene repression. So it can regulate gene expression. Histone modifications means acetylation and deacetylation of histone proteins by histone acetyltransferases (HATs) and histone deacetylases (HDACs). Acetylated histones are associated by increasing transcriptional activity and the reverse action if define for deacetylated histones. Micro RNAs or non-coding RNAs are the types of RNA that are not involving the protein coding. They are just regulator of gene expression (Wu and Zhao 2018).

In critically ill patient dysregulation of the mechanisms involving in epigenetics cause cell damage, multi organ failure and at last mortality. So some of the important epigenetic based prognostic and diagnostic biomarkers can be useful in predicting MODS (Crimi et al. 2019).

Postoperative pain known as a major stress factor that affect surgical prognosis. This factor can be converted to chronic type that means prolonged sympathetic and hormonal stress response in body. Chronic post-surgical pain (CPSP) is the pain that lasts for more than 2 months after surgery. In children the incidence of CPSP has a variety range of 13–68% in united State (Chidambaran et al. 2017c). But why in one patient acute post-operative pain converted to CPSP and in another patient it would not happen? Interindividual differences in incidence of CPSP was studied. In one of them it was correlated to DNA methylation of μ-1 opioid receptor gene (OPRM1) that code the main receptor which is identified as binding region of opioids. In fact, in this study they found that inhibition of DNA methylation can increase the OPRM1 gene expression and decrease the response to opioids (Chidambaran et al. 2017c). Other epigenetic mechanisms seems (seem) to be related to pain sensation like polymorphism involving the serotonin 5HT2A receptor, serotonin transporter and dopamine-4 receptor (Kaye et al. 2019).

Neurotoxicity and neurocognitive disorders after exposure to anesthetic drugs still remain a big concern especially in developing brains. In recent studies there are evidences that epigenetic related mechanism can explain neurotoxicity in human and animal neurons. These mechanisms include DNA methylation, histone modifications and non-coding RNAs. And of course one more step, they found that DNA methyltransferases (DNMTs) inhibitors and histone deacetylases (HDACs) inhibitors which reduce the activity of the first two mechanisms have therapeutic potential for decreasing post-operative neurotoxicity (Wu and Zhao 2018).

In stressful situations like a surgical procedure one of the important hormones that can make an enormous response is Adrenocorticotropic hormone (ACTH). It is produced in anterior pituitary gland cells and is regulated by corticotropin releasing hormone (CRH), vasopressin and catecholamine. The mechanism of the regulation of ACTH by these products is affecting the gene expression of Proopiomelanocortin (POMC) that is cleaved to variety of neuroendocrine peptides like ACTH. In animal studies there are evidence that benzodiazepines, opioid related drugs and high concentration of local anesthetics can increase POMC gene expression (Ikeda et al. 2007; Mahmood et al. 2019; Matyal et al. 2014). On the other hand, there are evidences show that some factors like exposure to alcohol in embryonic period and early neonatal can influence POMC gene expression in whole life (Bekdash et al. 2014). So identifying POMC activity in patients and a good drug selection for anesthesia maybe could attenuate stress response.

Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) is one the most important protein that can regulate mitochondrial activity. PGC-1α up regulated by sirtuin 1 (SIRT1) and mitogen-activated protein kinase (MAPK). Decreasing in expression of these proteins can decrease the level of PGC-1α which not only cause a dysfunction in fatty acid metabolism but also can increase inflammatory response in acute stress like a cardiopulmonary bypass surgery. Evidences

show that these proteins significantly decrease in diabetic heart before and after CPB and suggest to use this evidence to improve perioperative cardiac health (Mahmood et al. 2019). In other studies, intracardiac stress response and inflammation in diabetic heart were also correlated by over expression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and NOX1 (Matyal et al. 2014; Yan et al. 2013; Fillmore et al. 2014).

Proteomics and Metabolomics

Proteomics is a field of science that studying the structure and function of proteins to describe that how the changes in their structures can affect their functions. These proteins can work as cytokines, receptors, enzymes, ion channels and transporters in our bodies that can be different in all people of the world. These differences relate to the protein synthesis not their genetic codes or gene expressions. Metabolomics and proteomics have almost the same concept. Proteomics refer to structural and functional proteins but metabolomics refers to low molecular weight compounds that affect cellular phenotype. These low molecular weight compounds can be produced by protein activities like enzymatic reactions. In fact, metabolomics is the result of proteomics.

As previously described there are many stress responses after a surgery or tissue injury. All the stress responses have protein or non-protein structures. Proteomics and metabolomics in precision medicine try to find any proteins or metabolites that help us to predict stress response postoperatively in each person. We know how to measure patients stress after surgery but we need to know that how we can predict this response in different patients by their proteins and metabolites and how we can control it. Identifying predictors can help us to know vulnerable patients who show more complications due to more stress response and maybe to control the response with more monitoring or preventive methods in individuals according to their necessity.

To better understanding investigations show that psychiatric morbidity increases with high preoperative HPA (Hypothalamus Pituitary Axis) function. Patients with higher preoperative cortisol level have more depression and anxiety disorders after abdominal aortic aneurysm repair in 9 months follow up. So preoperative cortisol level can be a predictor of postoperative mood disorders (King et al. 2015).

In colorectal cancer surgery many investigations show that level of Tumor Necrosis Factor α (TNF α), Interleukin 6 before surgery and c-reactive protein to albumin ratio in the first day after surgery could be useful biomarkers for predicting post-operative infections (Goulart et al. 2018; Liu 2018; Labgaa et al. 2016). In a systematic review C-Reactive Protein level was known as a predictive biomarker for post-operative delirium (Ayob et al. 2019).

Among all post-operative complications some of them are more critical and important to know. Atrial fibrillation is one of the most common arrhythmia that happen after cardiac surgery and can increase morbidity and mortality significantly.

So the ability to predict high risk patients perhaps can help us to decrease mortality by additive monitoring and preventive treatment. There are associations between new onset post-operative atrial fibrillation and markers of extracellular matrix turnover like PICP (carboxy terminal propeptide of collagen I), PINP (amino terminal propeptide of collagen I), PIIINP (amino terminal propeptide of collagen III); markers of myocardial stretch like BNP (B-type natriuretic peptide) and markers of inflammation like CRP and IL6 (Turagam et al. 2016). All of these are reported in a few researches so in future if we could find the most related biomarkers to new onset post-operative atrial fibrillation maybe we could have cardiac surgery with better prognosis.

And this is just about one complication. Imagine 1 day we could control all post-operative complications by predicting and preventing them to happen.

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Chapter 14
Cellular and Molecular Basis of Regional Anesthesia and Acute Pain Practice and Applications to Personalized Medicine

Paul Guillod and A. Sassan Sabouri

Introduction

Personalized Medicine

Personalized, or precision, medicine describes an approach to disease prevention, diagnosis, and treatment that seeks to maximize treatment effectiveness and minimize unintended or adverse effects by incorporating an individual's variability in genes, environment, and lifestyle in a sophisticated data-driven manner (Ginsburg and Willard 2009).

Over the last few decades, there has been an explosion in genomic, molecular, and cellular biology data combined with advances in medicine which stand to revolutionize health care treatments and outcomes. Genetic data can be used to better design a study or to identify the subgroup of patients who may obtain the maximum benefit from a treatment with minimal toxicity. This also changes how health and disease is classified. To this end, the National Academy of Sciences committee published a framework for integrating genomics, proteomics, metabolomics, and other data sources into a new taxonomy disease which naturally gives way to personalized medicine (National Research Council Committee on 2011).

This step forward in medicine has only recently been possible with advances in areas like molecular biology, novel biomarker identification, high throughput drug

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development, cost reductions in sequencing, and data science alongside electronic medical records which establish meaningful relationships with longitudinal analysis.

While personalized medicine can be broken down in various ways, recognized principal areas are:

1. Genomic medicine, which refers to defining penetration of different genetic mutations and pharmacogenomics
2. Molecular medicine, which is related to the molecular-based mechanism of disease and therapeutics
3. Data Science, which might include risk stratification and the application of electronic health records (EHR) and genomics for prediction of a pathologic state
4. Implementations Science, which integrates the domains of precision medicine, genomic and biomarker data in the healthcare setting (Table 14.1).

The tools of precision medicine, or resources that are incorporated include:

1. DNA array genomic, genotyping and sequencing of disease state
2. Correlating the pathologic states with biobanks
3. Electronic health records with other digital technologies
4. Big data methods and machine learning with artificial intelligence
5. Phenotyping
6. Large multicenter clinical trials.

While still a burgeoning medical discipline, there are many areas where personalized medicine is currently being used, perhaps most notably within medical oncology where an individual's tumor genetic mutation profile can be sequenced and used for precise therapeutic targeting (Papaemmanuil et al. 2016; Grinfeld et al. 2018; Schmitz et al. 2018). Precision medicine may also find an impact in areas of medicine like psychiatry where treatments are often trial-and-error through classes of medications while pharmacogenomics could tailor empiric treatment (Ozomaro et al. 2013; Torres et al. 2016).

Another area where personalized medicine is being realized is in the identification and validation of new targets in drug developments through accurately modeling cellular and molecular interactions. Incorporating genetically-supported targets allows for designing and tailoring novel therapeutics (Dugger et al. 2018). Large computational workflows that incorporate next-generation sequencing, functional

Table 14.1 Resources of personalized medicine

Category	Definition
Genomic medicine	Defining penetration of different genetic mutations and pharmacogenomics
Molecular medicine	Molecular-based mechanism of disease and therapeutics
Data science	Application of electronic health records (EHR) and genomics for prediction of a pathologic state
Implementations science	Integrates the domains of precision medicine, genomic and biomarker data in the healthcare setting

proteomics, and molecular network analysis could comprehensively overhaul our approach to discovering new medicines (Lippmann et al. 2018).

One of most exciting area of precision medicine is in using genomics to build a genetic risk score (GRS) model for predicting disease and treatment response. The GRS model has been used in coronary heart disease (CAD) in select epidemiological cohorts. For instance, a population with high GRS for CAD may benefit from statin therapy (Mega et al. 2015). This approach to treatment represents a turn from clinical heuristics, or decisions based on rudimentary divisions or flow charts derived from limited studies, to real-time data-driven risk profiles and therapeutic recommendations.

Toward this future care model, the NIH through the National Human Genome Research Institute created the Electronic Medical Records and Genomics (eMERGE) network to fund cross-institutional research combining biorepositories with EHR systems for genomic medicine (McCarty et al. 2011) which aims to "develop and validate electronic phenotyping algorithms for large-scale, high-throughput genomics research." Other public consortiums are also collecting and integrating pharmacogenomic data such as PharmGKB (Whirl-Carrillo et al. 2012).

Personalized Medicine in Regional Anesthesia

There are many potential future applications of personalized medicine within the field of Anesthesiology. This chapter focuses on exploring that topic with regard to perioperative pain management using regional anesthesia, an established and growing subdiscipline that focuses on the relief of perioperative/surgical pain primarily through the inhibition of nerve transmission. Good pain management in the perioperative setting does more than relieve the inconvenience of pain, it reduces the body's stress response to surgery which has many benefits, such as even reducing the risk of post-op MI (Beattie et al. 2001).

The goal of this chapter is to discuss principles of regional anesthesia and its potential applications in personalized medicine by exploring the genomics of pain, basis of nociception and peripheral nerve anatomy, the cellular/molecular mechanisms of local anesthetics, and the role of regional anesthesia in surgical oncology.

Personalized medicine within regional anesthesia is still very new with much left to speculation at this juncture. It is likely that pharmacogenomics will be a small aspect of personalized regional care.

Brief History of Regional Anesthesia

The purpose of regional anesthesia is to eliminate pain through the direct inhibition of nerve transmission. By stopping the noxious signal, we can eradicate the sensation of pain and limit the sympathetic response to injury. This signal intervention

can be through basic tissue infiltration, perineural injections, or neuraxially at the level of the spinal cord. The role and specificity of regional anesthesia has greatly expanded with our understanding of nerve anatomy and physiology, molecular basis of nociception, and real-time targeting ability through ultrasound.

Before the discovery of local anesthetics (LA), the only means to establish a peripheral nerve block were direct compression of the nerve or the application of ice which were ineffective and prone to injury. While the full history of regional anesthesia can be gleaned from more comprehensive sources, it helps to have a perspective which we will outline here.

Regional anesthesia had its advent in the late nineteenth century with the discovery of local anesthetics, the first of which being cocaine, an extract of coca leaves long known to produce a numbing sensation when chewed on (along with its more notorious stimulant effects). Ether had only been recently discovered, but already general anesthetics were decidedly not ideal in dentistry and for certain surgeries, especially when emergence followed with retching.

While there were many scientists, dentists, and physicians involved in the research of cocaine as a topical anesthetic, the first recognized use occurred in 1884 by Koller (Calatayud and González 2003) who administered topical cocaine for ophthalmologic surgery, a procedure that benefits from an awake, directable patient. Along with the invention of the hypodermic needle and syringe, cocaine was soon expanded from topical use to skin infiltration, peripheral nerve blockade, and the first spinal and epidural injections—each method discovering its effective dose, toxicity, and, unfortunately for cocaine, dependence. While intravenous injection proved to be short-lived as a regional technique, Bier introduced a tourniquet that prolonged its duration still in use today.

Cocaine was the exclusive local anesthetic for around 20 years until the synthesis of amylocaine (Stovaine) in 1903 and procaine (Novocain) the following year. Lidocaine, the best known and most used local anesthetic, was not introduced until around 1947. By then, scientists recognized the helpful categories of local anesthetics based on whether they had an amide or ester bond, with the esters having worse shelf-life, duration of action, and the occasional allergic reaction to the otherwise non-toxic by product para-aminobenzoic acid (PABA). Research focused on developing amide anesthetics with mepivacaine and bupivacaine introduced in the 1960s. Modifications and enantiomer separation led to ropivacaine and levobupivacaine introduced in the 1990s as less cardiotoxic alternatives to bupivacaine. Research continues in synthesizing novel local anesthetics.

Regional anesthesia as a field has markedly evolved as well. As our understanding of spinal and peripheral nerve anatomy advanced, so did the neuraxial and peripheral block techniques. Landmark based nerve localization developed in conjunction with nerve stimulators and were used for most of the twentieth century, often requiring large injectate volumes and passing the needle through large arteries. These days, ultrasound has greatly increased the precision and targeting of peripheral nerves, affording a durable block with lower injection volumes and lower risk of nerve injury.

Regional techniques have been established as a preferred anesthetic when possible. In the ASA Practice Guidelines for Acute Perioperative Pain Management (2012), regional approaches conferred improved pain scores across studies and when polling anesthesiologists, 95% agreed or strongly agreed that a regional block should always be considered with multimodal pain management.

Principles of Pain Transmission

Peripheral nerves carry sensory input, motor output, and sympathetic innervation. In general, local anesthetic agents act most potently on sympathetic nerves followed by sensory nerves and finally motor nerves. This variable effect leads to what is known as a differential blockade. Much of this can difference be explained by the respective nerve properties which are: fiber type, diameter, conduction, and myelination. The local anesthetic choice also plays an important role in the degree of differential block (Gissen et al. 1980; Rosenberg and Heinonen 1983). Fiber types are categorized by their average diameter using the Erlanger-Gasser classification of A, B, and C with A having subtypes α, β, γ, and δ. Type A are myelinated with the largest diameter and fastest conduction while "type C" are unmyelinated with the smallest diameter and slowest conduction velocities.

Primary sensory neurons, the first order afferent input, have their cell bodies in the dorsal root ganglion (DRG) with a distal axonal extension to the skin periphery and the other end synapsing in the dorsal horn of the spinal cord. Sensory input is delivered via Aβ, Aδ, and C fibers. Aβ fibers compose light touch and pressure, Aδ compose pain (fast) and temperature, and C fibers carry the largest population of nerves relaying pain.

When primary nociceptors are activated, the sensory neurons release a cascade of molecules at their synapse in the spinal cord including Substance P (SP), calcitonin gene-related peptide (CGRP), and glutamate. The sensory neurons also release molecules at their peripheral terminals including SP which acts through the Neurokinin 1 receptor (NK_1) causing vasodilation and local inflammation. There are also many local signaling molecules that can influence the activity of nociceptor fibers.

Much of the research on inflammatory pain states have shown that C fibers have receptors for many cytokines such as TNF-a, IL-1b, and IL-17 (Schaible 2014) that can induce sensitization through upregulation of TRPV1, a non-selective ion channel which is responsible for transducing thermal and mechanical pain. This channel is also known to be activated by capsaicin. There is ongoing research into TRPV1 and NK_1 receptor antagonists to counteract this sensitization which may find use within regional anesthesia for patients with chronic pain states. Perhaps measuring an individual's cytokine expression profile could aid in identifying personalized regional treatments when patients undergo surgery.

Individual Differences in Response to Pain/Perioperative Pain Genomics

Although tissue damage and activation of pain receptors is the first step in the cascade of noxious stimulation, the degree of pain for the same insult varies significantly between subjects, thus important and inseparable part of a pain phenotype is to show the individual variability and difference in sensitivity. Pain sensitivity measurements largely derive from animal models given the controlled setting. There is substantial evidence that pain sensitivity in these experimental measures is related to degree of pain, however, lack of control over degree of noxious stimulus is a considerable limitation of these studies (Verne et al. 2001; Carli et al. 2002; Petzke et al. 2003; Giesecke et al. 2004a, b; Staud 2010).

On the other hand, using electronic medical health records to gather large and heterogeneous population based data with wide and diverse pain sensitivities may overcome the discrepancies across types of pain. One may assume that different pain phenotypes may have one underlying dormant hidden phenotype supported by multiple single-nucleotide polymorphisms (SNPs). This approach has been used in twin studies where the hidden phenotype explained 95% risk of developing pain in separate parts of body (Williams et al. 2004).

In the situations where the pain condition does not involve a clear tissue pathology, or idiopathic/dysfunctional pain, the presence of many environmental contributors affect the pain phenotype significantly, with phenotypic changes as the disease progress (Linnman et al. 2011).

Most pain syndrome phenotypes are complex, and their inheritance do not follow the Mendelian patterns. However, research in rodents and human twin studies have shown considerable invertibility of nociception, clinical pain syndromes, sensitivity to pain, and response to analgesics (Diatchenko et al. 2006; Fillingim et al. 2008; Lacroix-Fralish and Mogil 2009; Angst et al. 2012; Mogil 2012). As expected, though, animal models don't reliably predict human responses to pain.

Interestingly, genetic influences on pain intensity can differ considerably based on the gender of the individual and the level of stress associated with the pain condition. There is evidence, for instance, that female gender is associated with more postoperative pain (Fillingim et al. 2009; Ruau et al. 2012b). A study using EHR on more than 11,000 patients showed that women report higher pain scores compared to men following similar diagnostic procedures (Ruau et al. 2012b). Using a mouse model, XX genotype and gonadectomized mice showed greater thermal and chemical nociceptive sensitivity and greater morphine resistance than XY mice. Whereas in the presence of gonads, XX mice showed more tolerance to morphine (Gioiosa et al. 2008). The relation to gonadal hormones, especially estrogen receptor genes on the pain intensity and analgesic responses has also been demonstrated (Craft et al. 2004). In a transgenic mice model, estrogen beta receptors (ERβ) demonstrated a pro-nociceptive role in both sexes (Coulombe et al. 2011). Using quantitative trait locus mapping (QTL)—a technique in which a trait gene can be located by using inheritance patterns, *Calca* or calcitonin gene-related peptide (CGRP)

encoding gene, was identified as a major genetic predictor for thermal nociception in mice and potentially humans. *Calca* is much higher in female mice than male (54 vs. 36% respectively) (Mogil et al. 2005).

However, studies on human pain genetics regarding gender associations are contradictory. For example, the A118G SNP opioid receptor Mu 1 (OPRM1) gene has been associated with more pressure-pain sensitivity in females than males (Way et al. 2009). COMT (Catechol-*O*-methyltransferase) genes were associated with higher pain scores in females but not in males (Fijal et al. 2010). In contrast, actin-binding LIM protein 3 gene is associated with cold-induced pain in males and not females (Ruau et al. 2012a). A study by Aoki showed that the serotonin 2A receptor gene (5-HTR2A) is associated with more analgesic requirements in women following abdominal surgery than men.

The effect of physical and psychological stress on pain related syndromes are well known. Stress as a factor for modulating pain can enhance or diminish pain sensitivity, therefore stress can cause stress-induced hyperalgesia or stress-induced analgesia (Imbe et al. 2006; Butler and Finn 2009). The presence of COMT variants has been shown to predict pain and psychological symptoms after motor vehicle collisions with the associated physical and psychological stress (McLean et al. 2011). Another study looking at SNPs in COMT showed that a homozygous variant group consumed almost 40% more opioids than their counterparts (Candiotti et al. 2014). However there are many more genes that relate to pain, opioid responses (Ren et al. 2015; Li et al. 2019) and experience even including immune cell Toll-like receptors with at least 640 genes found to date that play a role in the experience and modulation of pain (Liu et al. 2012; Peirs and Seal 2015; Bagheri et al. 2016; Sezari 2017; Lippmann et al. 2018; Zali et al. 2019).

Organization and Ultrastructure of the Peripheral Nervous System

Histology and Electron Microscopy of Human Peripheral Nerves System

In the last few decades, the detailed structure of the peripheral nervous system has been shown through anatomic dissections with histological and electron microscopy. The electron microscope has added more detailed information on the ultrastructure and histological details of the peripheral nervous system. Some of the highlighted details of this ultrastructure may be meaningful to the future practice of peripheral nerve blocks.

The peripheral nervous system (PNS) includes neurons with various functions, somatic and autonomic. The basic functional unit of the nervous system is the neuron. Neurons are supported by other nervous system cells called neuroganglia. Each neuron is composed of a cell body, dendrites, and a single axon.

The *cell body* or *soma* or *perikaryon* is the most conspicuous part of a neuron and usually with a prominent spherical or ovoid nucleus. The neuron cytoplasm includes rough endoplasmic reticulum (RER) with many cisternae and polyribosomes. When polyribosomes attach to the RER, they produce *Nissl bodies*, which are even visible with a light microscope. In the axon hillock, the region of soma from which axon rises, smooth endoplasmic retinaculum (SER) replaces the RER. Another prominent part of cell body is the *Golgi apparatus*, the protein secreting part of the cell and in charge of neurotransmitter packing. Numerous mitochondria are scattered in the cytoplasm and even more abundant at axon hillock. Electron microscopic details of cytoskeletal components reveal three different filamentous structures: microtubules (up to 24 nm diameter), neurofilaments (10 nm diameter) and microfilaments (6 nm diameter).

Axons are the cellular projections that run from a source to target by conducting current. These axons are arranged in a hierarchical manner with groups of efferent motor axons, afferent sensory axons, and sympathetic fibers.

Electron microscopic examination of myelinated axons has shown that each axon has a very dense cytoplasm with mitochondria, microtubules, lysosomes, neurofilaments, cisterns of cytoplasmic reticulum and cytoplasm.

Axons start from axon hillock as a single thin process and can be extended over a meter. Axon thickness directly correlates with its velocity, or that the diameter increases as current velocity increases. *Axoplasma* or cytoplasm of an axon is a very thin and dense layer. This area of axon has no RER but has numerous microtubules and neurofilaments.

The axons can be divided into myelinated and unmyelinated. Neuronal axons are myelinated by *Schwann cells* which run along the nerve tracts and wrap the axon in a myelin sheath (Fig. 14.1). All the motor neurons and some sensory neurons are myelinated.

Schwann cells are only located in the PNS. They are flat cells including a flattened nucleus. Electron microscopy has shown that myelin is actually the plasmalemma of the *Schwann cell* that is wrapped several times around the axon. Interruption of this sheath occurs at points along the axon called *nodes of Ranvier* which are the interface between two adjacent *Schwann cells*. Each *Schwann cell* and its associated nodes of Ranvier is covered by a basal lamina. The basal lamina functions as the regenerative guide following nerve injury. *Schwann cell* cytoplasm can be trapped into the lamellae of the myelin creating a cone-shaped cleft in the myelin sheath of each internodal segment known as a *cleft of Schmidt-Lanterman*. Narrow outer leaflet of *Schwann cell* plasma membrane is call *intraperiod line*. High resolution electron microscope has shown small gaps in this line between layers of myelin which is called *intraperiod gaps*. The gaps are potential access for small molecules to reach the axon.

Unmyelinated axons are not covered with myelin sheath but 6–8 of unmyelinated axons can be associated with one *Schwann cell* that separates these axons from each other. Although sometimes one unmyelinated axon may be surrounded with one single layer of *Schwann cell* (Fig. 14.2) (Chen et al. 2011; Reina et al. 2013).

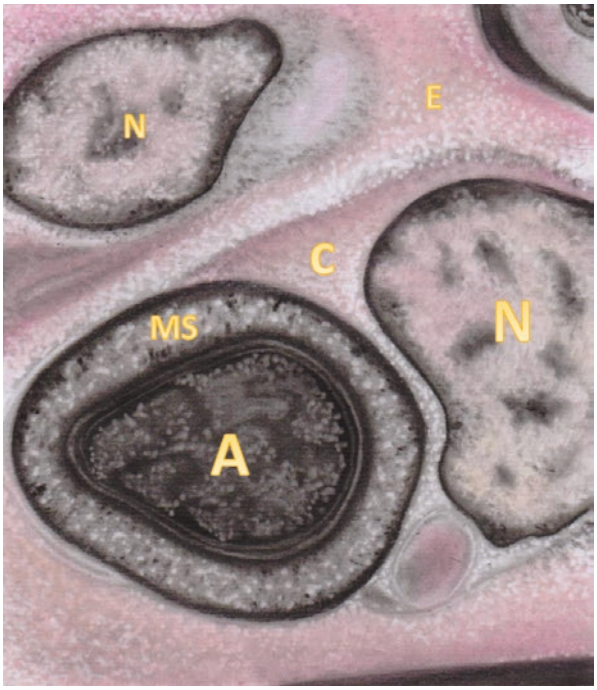

Fig. 14.1 Graphic image of an electronic microscopic picture of myelinated axons (A) with Schwann cells (C) wrap around the axon. MS: Myelinated Sheaths, A: Myelinated Axon, N: Schwann cell Nucleus, E: Endoneurium C: Cytoplasm of Schwann cell

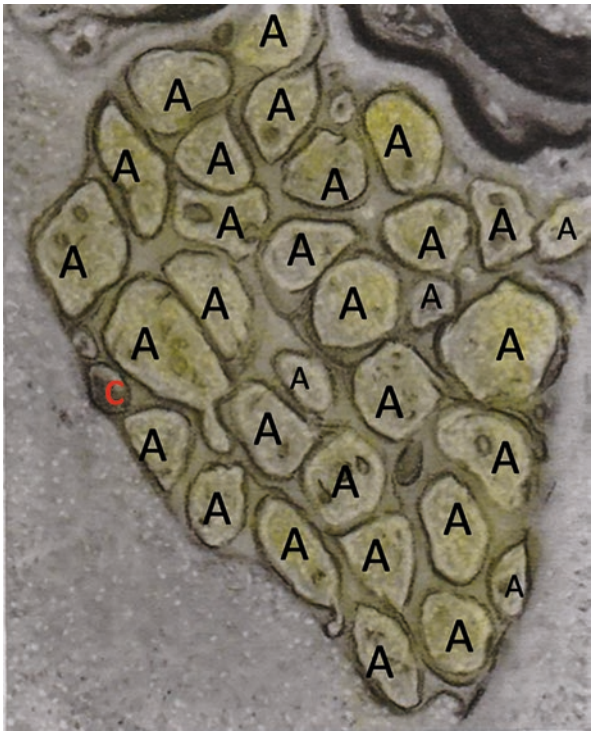

Fig. 14.2 Graphic drawing of an electron microscope image of an unmyelinated axons (A). A group of unmyelinated axons may accompany with a Schwann Cell (C)

Synapses

Synapses are the sites where nerve currents are transmitted from a neuronal source (presynaptic) to ass receiver (postsynaptic) neuron, muscle cell, or gland cell. At each synapse, the presynaptic neurons form a bulbous expansion at the end of an axon or dendrite called the *bouton terminal* or *boutons en passage*. Different types of synapses are explained in Table 14.2.

The cytoplasm at the presynaptic membrane contains SER, many synaptic vesicles and many mitochondria. Synaptic vesicles are oval, 40–60 nm in diameter, and contain neurotransmitters to be released. Cell membrane close to a synapse has a cone-shape projection toward the postsynaptic membrane and forms the active side of the synapse where the vesicles are released. Synapsin I is a complex protein that helps to hold the synaptic vesicle in the active site. Phosphorylation of this protein determines the transmission direction. Synapsin II is another protein which controls the vesicles with microfilaments. Other synaptic proteins that help unloading neurotransmitters are synaptotagmin and synaptophysin.

The postsynaptic membrane is a thickened portion of receiving cell membrane which contains the neurotransmitter receptors.

Peripheral Nervous System

Peripheral nerves are composed of bundles of nerve fascicles extended outside of the CNS. The nerve fascicle is the functional unit of a nerve and consists of a group of axons covered by *endoneurium* and packed within another layer, the *perineurium*.

Endoneurium is the innermost layer of connective tissue that surrounds each axon and Schwann cell. *Endoneurium* is composed of reticular fibers, macrophages, capillaries, mast cells and fibroblast cells and serves as a separation compartment of each nerve.

Perineurium covers each bundle of nerve fascicles and is composed of a thin connective tissue with several layers of epithelioid cells joined together by *zonulae occludentes* and basal lamina. This layer is an isolation layer which is also called *blood-nerve barrier*.

Epineurium consists of connective tissue and vessels which cover all of the fascicles. *Epineurium* is composed of dense, irregular and collagenous connective tissue. This layer becomes thinner as nerves branch to more distal and smaller nerves.

Table 14.2 Types of synapses

Name	Type
Axosomatic synapse	Synapses between axon and a soma
Axoaxonic synapse	Synapses between two axons
Axodendritic synapse	Synapses between axon and dendrite
Dendrodendritic synapse	Synapses between two dendrites

Microanatomy and Interneural Topography of Brachial Plexus

Microscopic examination of the brachial plexus has shown significant differences and complicated structure in histologic appearance from the interscalene region to the axilla. The level of the cords, the nerve elements are relatively isolated. However, bifurcation and recombination of the fascicles happen at the level of the trunk. As the brachial plexus progresses toward more division and cords, the number of fascicles increase and spread into a wider space (Fig. 14.3) (Chen et al. 2011).

Microanatomy and Interneural Topography of Sciatic Nerve

Topographic maps of the sciatic nerve showed that this nerve and its branches vary. This variability is due to exchange of axons which start at the level of the dorsal root and continue along the main trunk. Number of nerve fascicles also increases along the course of the nerves (Sunderland and Ray 1948) (Fig. 14.4). Sciatic nerve at the level of popliteal fossa is supported by perineurium in connection to epimysium, whereas each group of fascicles is mainly filled with fat and collagen tissue.

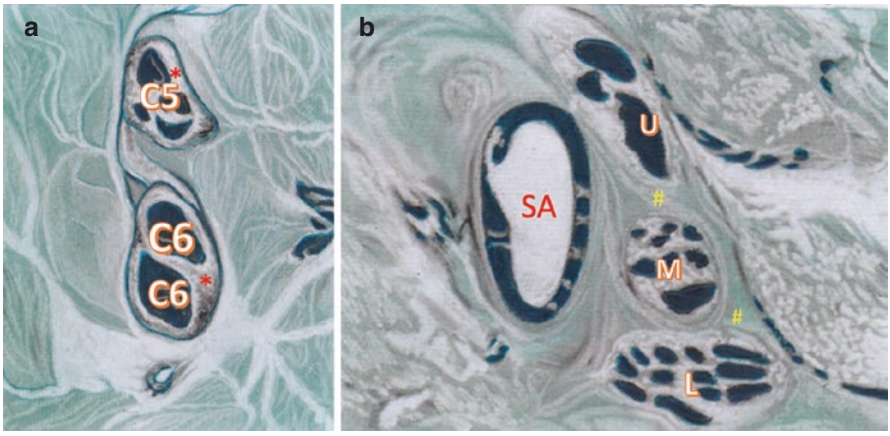

Fig. 14.3 Schematic image of the difference in appearance of brachial plexus at the C5 and C6 roots (**a**) and Trunks (**b**) – At the level of the trunks more prominent perineurium (*) tissue is noticed whereas at the level of the trunks more interstitial tissue and adipose (#) tissue fills the intertruncal planes. U: Upper Trunk, M: Middle Truck, L: Lower Trunk, SA: Subclavian Artery

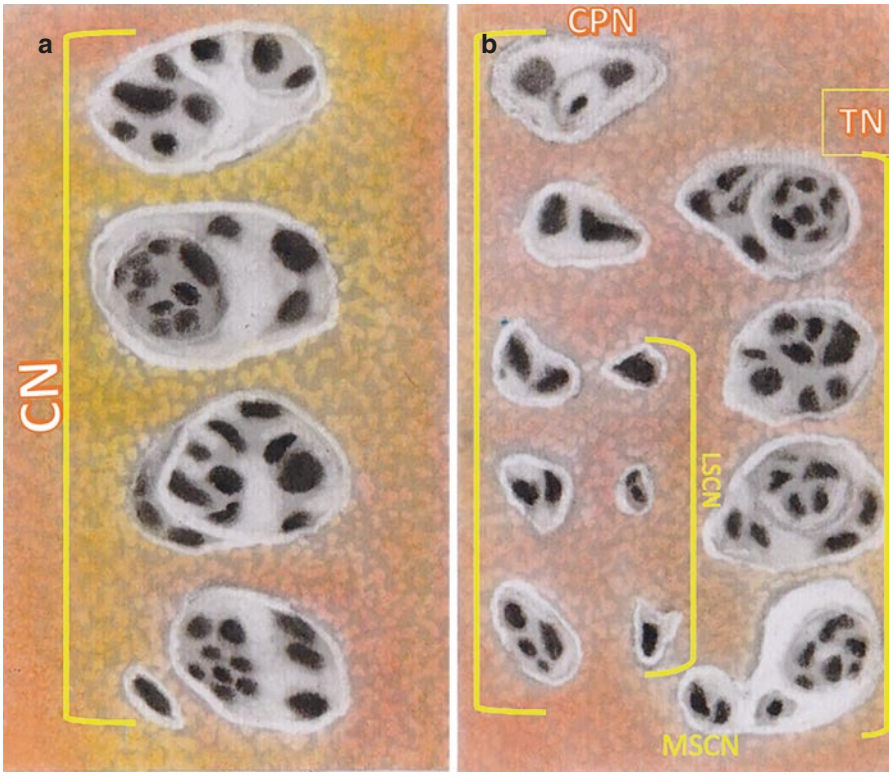

Fig. 14.4 Graphic image of the cross-sectional histology of A- human sciatic nerve (CN) and B- its branches in their course from the popliteal fossa to proximal leg. Common Peroneal Nerve (CPN), Tibial Nerve (TN), Lateral Sural Cutaneous Nerve (LSCN) and Medial Sural Cutaneous Nerve (MSCN)

Molecular Basis of Regional Anesthesia

Local Anesthetics

Local anesthetics (LA) are the primary pharmacologic category used in regional anesthesia as they induce complete, reversible interruption in nerve transmission.

Local anesthetics consist of hydrophilic (amine) and hydrophobic (aromatic ring) ends linked by an ester or amide bond. The type of bond divides the two classes of LAs as it reflects their metabolism. Amino esters are rapidly metabolized by plasma pseudocholinesterases while amino amides are metabolized by the liver cytochrome P450 system, generally CYP3A4 and CYP1A2 (Oda et al. 1995; Wang et al. 2000).

The amine group on LAs make them weak bases which at physiologic pH predominate in a protonated amine/charged form that cannot penetrate cell membranes.

Uncharged forms however readily cross cell membranes to their site of action. Each LA has its own pKa, usually around 8–9. As the pKa decreases, the speed of onset increases as a higher proportion will be in its diffusible, uncharged form. The aromatic ring can additionally host lipophilic R-groups that increase its potency so that it passes more easily through neuronal membranes allowing lower concentrations to be used (Becker and Reed 2012). The duration of a block generally relates to its degree of protein binding and the inclusion of a vasopressor such as epinephrine that limits local clearance.

In other words, local anesthetics can be engineered to have specific onset, duration, and potency. However, such modifications can have other effects such as the amount of local vasodilation, degree of differential block, and toxicity profile. The worst complication of local anesthetic systemic toxicity (LAST) is complete cardiovascular collapse that is heralded by convulsions. Fortunately, this complication is exceedingly rare. In an 8 year study on 12,668 patients receiving peripheral nerve blocks there was 1 seizure and 0 cardiac arrests (Sites et al. 2012). One way to limit the absorbed dose and prolong the block is through new delivery vehicles such as with liposomal bupivacaine (Malik et al. 2017).

Local anesthetics act on voltage-gated sodium channels (VGSC). VGSCs are densely populated along the entire length of unmyelinated axons and concentrated at nodes of Ranvier in myelinated axons. The VGSC exists in 3 conformational states: activated/open, inactivated, and resting/closed. LAs bind the cellular side inner pore in domain IV S6 of the channel during depolarization, leading to what is known as a state-dependent block (Strichartz 1976; Fozzard et al. 2011). When open, the channels allow sodium ions to flow down their concentration gradient propagating an action potential which is blocked by local anesthetic binding.

There are 9 VGSC isoforms in humans, regulated and expressed by tissue type and divided into tetrodotoxin sensitive and resistant (Novakovic et al. 2001). The full functional structure of VSGCs are still being elucidated, but as our understanding of theses intricate ion channels improve, we may be able to engineer new drugs that antagonize the receptor at unexplored binding sites (Lai and Jan 2006), perhaps in combination with local anesthetics that work synergistically at significantly lower doses. There are even proposals to create channel isoform specific antagonists for controlling syndromes like chronic cough (Muroi and Undem 2014).

Outside of action on VGSC, local anesthetics have both demonstrated and postulated roles in other pathways and receptors such as on protein kinases, calcium signal modulation, and G-protein coupled receptors (Nivarthi et al. 1996; Hollmann et al. 2001; Xu et al. 2003).

Current dose limits for local anesthetics to mitigate risk of toxicity tend to be overly conservative and not empirically based with data derived from single clinical events and animal data (El-Boghdadly et al. 2018). Furthermore, the site of LA injection has a large influence on the rate of uptake and peak plasma concentration (de Jong and Bonin 1980). Combined with differences in liver metabolism, drug-drug interactions, and ion channel genetic variations, there are many variables that can influence peak plasma concentration. Even what concentration causes side

effects is unclear. Perhaps one area of personalized regional anesthesia will be in establishing local anesthetic maximum doses.

One interesting area of research with novel local anesthetics is investigating charged quaternary ammonium LAs such as QX-314. While charged molecules take a long time to cross the neuronal membrane, there is nevertheless a slow onset but long lasting effect with them (Lim et al. 2007). Even more intriguing, in combination with capsaicin QX-314 can produce a sensory specific block. The TRPV1 receptor can be found on C pain fibers and activates in response to capsaicin. One group demonstrated that performing a block in animals with QX-314 followed by capsaicin 10 min later at the same site produced a dense sensory specific block. The hypothesis is that the TRPV1 receptor activation facilitates entry of QX-314 into the cell where it is able to have a fast and sensory specific onset (Gerner et al. 2008). Further analysis of membrane proteins and channels throughout peripheral nerves will further refine the ability of regional anesthesia to target nerve types precisely.

Adjuvants

While local anesthetics are the principal drug used in regional anesthesia, there is ongoing research on the utilization of adjuvant medications for use in peripheral and neuraxial blocks. Local anesthetics have a limited duration of action and dose dependent adverse events. Adjuvants have been used to synergize the effect and prolong block duration. Epinephrine is the most familiar co-administered drug with LA which causes vasoconstriction that limits systemic absorption. Another class of medication used to facilitate regional anesthesia are α_2 agonists such as clonidine or dexmedetomidine. There have been trials with many classes of medications with varied results including steroids, anti-inflammatory agents, ketamine, benzodiazepines, and even neuromuscular blockers (Swain et al. 2017).

Role of Regional Anesthesia in Oncology

As we have come to understand, surgery and medications used in anesthesia can have profound effects on the function of the immune system. This is particularly relevant in surgical oncology. Studies have shown that there are many perioperative factors that can contribute to immune suppression such as the stress response, opioids, volatile anesthetics, blood transfusions, hypothermia, and inadequate pain control. Surgery itself is associated with decreased immune function due to pain, stress, and tissue damage, and can even trigger metastases as first demonstrated in mice (Shapiro et al. 1981; Kurz et al. 1996; Page 2005; Stollings et al. 2016; Tohme et al. 2017).

Recurrence and spread are particularly worrisome because the introduction of tumor cells into circulation depends on host defenses, specifically natural killer (NK) cells and macrophages, as the primary immune cells against cancer. Multiple perioperative factors help limit the degree of spread and recurrence. Factors that can

accelerate the spread of cancer include shedding of the cells into the blood and lymphatic system at the time of tissue trauma, increasing cancer cell growth factors such as TGF-β and catecholamines, and increasing pro-angiogenic factors such as VEGF. The surgery itself induces a neuroendocrine response with the release of several cytokines. In the early phase of cell trauma, there is a release of pro-inflammatory cytokines including IL-1, TNF-α inducing a leukocytosis. In the latter phase, depression of both acquired and innate immune function predispose the patient to sepsis, nosocomial infections, and tumor growth (Denstaedt et al. 2018).

Fortunately regional anesthesia has emerged as a potential factor that can mitigate the degree of immune suppression by reducing the stress response and the need for post-operative opioids which themselves can inhibit innate and adaptive immune function (Sacerdote et al. 2000). Spinal anesthesia in patients who undergo transurethral resection of the prostate has been shown to increase T-helper 1 (Th1) cells which produce interferon and support cell-mediated immunity with T-helper 2 (Th2) cells which produce IL-4 and propagate the humoral immunity improved compared to patients who undergo the same procedure under general anesthesia (GA) (Le Cras et al. 1998).

Wada et al., also showed that addition of addition of spinal anesthesia to GA attenuates the suppression effect of GA on tumoricidal function of the liver mononuclear cells, presumably by preserving the Th1/Th2 balance and thereby reduces the promotion of tumor metastasis (Wada et al. 2007). One study on using a paravertebral block (PVB) after breast cancer surgery also showed that a PVB led to greater natural killer cell activity compared to those who had GA which may affect recurrence or metastasis (Exadaktylos et al. 2006; Gottschalk et al. 2010; Buckley et al. 2014). Combination of epidural analgesia with GA has also been shown to reduce the change of cancer recurrence in patients with prostate cancer (Exadaktylos et al. 2006). However it was controversial to show any effect on recurrence of colorectal cancer (Gottschalk et al. 2010; Cummings et al. 2012).

Going further, a retrospective study of patients undergoing resection for head and neck cancers compared cervical epidurals with GA to GA alone and showed that the 5 year survival was higher in the group with an epidural (68% compared to 37%). Another retrospective study of 50 women undergoing mastectomy for breast cancer compared GA with or without a paravertebral block, showed that recurrence and metastasis free survival at 36 months was 94% in the paravertebral group and 77% in the general anesthesia only group (Exadaktylos et al. 2006). Another retrospective study compared GA with and without an epidural in patients undergoing radical prostatectomy, the epidural group had a 57% lower risk of cancer recurrence compared with general anesthesia with opioids (Biki et al. 2008). Generally, when things sound too good to be true, they are, and in fact a recent randomized controlled study by Sessler, et al. looked at 2132 women undergoing surgery for breast cancer comparing PVB with GA with regard to cancer recurrence and did not show significant differences in survival or recurrence (Sessler et al. 2019).

Another area of influence in oncology is the chemotherapeutic effects of local anesthetics. In vitro, lidocaine has been shown to enhance NK cells via the release of lytic granules (Ramirez et al. 2015).

Chronic inflammation can induce DNA damage and is thought to contribute to 25% of cancers (Kawanishi et al. 2017). Increased tumor multiplicity secondary to hormonal mediators such as Src tyrosine protein kinase, which is involved in inflammatory signaling, has been shown to have a crucial role in solid cancer metastasis (Meira et al. 2008). Src tyrosine protein kinase is involved in signaling epithelial cell to mesenchymal transformation, promoting cell survival and mitogenesis and has significant effect on the cytoskeleton remodeling for cell migration necessary for tumor metastasis (Liu et al. 2013). Intercellular Adhesion Molecule 1 (ICAM-1) is a surface glycoprotein which is typically expressed on endothelial cells and cells of the immune system. Increased level of ICAM-1 is associated with an aggressive tumor expression. In addition, ICAM-1 expression is associated with a reduction in the disease-free interval in patients with liver metastasis, breast cell carcinoma, and gastric cancers (Kageshita et al. 1993; Maruo et al. 2002; Rosette et al. 2005).

The effect of amide linked local anesthetics on the non-small cell lung cancer (NSCLC) NCI-H838 lung cancer cells showed that ropivacaine and lidocaine decease ICAM-1 phosphorylation and Src activation in a dose-dependent manner (Piegeler et al. 2012). The effect of ropivacaine and lidocaine on the migration of NSLC cells was also inhibitory. However, these effects has not been observed with ester linked LAs. Intravenous lidocaine can also suppress inflammatory mediators such as IL-1 which indirectly helps immune function (Yardeni et al. 2009).

In summary, regional anesthesia and prevention of the inflammatory response can enhance immunity and prevent cancer expansion. Local anesthetics, especially amide based, have a direct effect on the modulation of the immune system and attenuate inflammatory responses. Although these effects may have beneficiary effects on the recurrence of cancer metastasis, further clinical studies are needed to clarify these findings.

Electronic Health Records and Machine Learning in Regional Anesthesia

Roughly 97% of US hospitals have reported using longitudinal records of patient medical and health history over the last 15 years. The role of EMR systems in changing health care cannot be overstated. Outside of its early goals of reducing errors, redundancies, cost containment, and compliance, one of the evolving benefits is clinical decision support and automation using passive or active support pipelines for enhancing clinical competency with regard to diagnosis and treatment plans (Appari et al. 2012, 2014; Rothman et al. 2012; Kharrazi et al. 2018).

Combining and linking the EMR with biobanks has created wide data rich networks such as eMERGE which includes records of 8.9 million patients with 600,000 cases of psychiatric disorders and genomic data up to 254,000 (McCarty et al. 2011).

This vast and continuously growing data can be too sparse and multidimensional to be wielded by simple hypothesis driven logistic regression. Instead large-scale analyses can be performed by machine learning. As machine learning algorithms

and natural language parsers become increasingly sophisticated and independent without model training, the developed AI will be able to perform real-time diagnostic and therapeutic risk estimates far exceeding today's capabilities.

Machine learning in regional anesthesia and pain medicine has already started to penetrate the field as a fast growing topic. It has been used to predict need for femoral nerve block after ACL repair or to predict requests for preoperative acute pain service consultation (Tighe et al. 2011, 2012a, b, c). Integrated data from ICUs, labs, and clinic notes to are also used to predict length of hospital stays and clinical needs (Gardner 2016).

EMRs combined with GRS may provide even more precision in prediction models. Some of the top research resources on large-scale bioinformatic include:

- Partner's Biobank with more than 100,000 genomic datasets (Karlson et al. 2016)
- the Million Veteran Program with 1,000,000 (Gaziano et al. 2016)
- "All of Us" with more than 1,000,000 (Denny et al. 2019)
- and the Biobank UK with 500,000 datasets for deep genetic and phenotypic data analysis (Kiryluk et al. 2019)

The "All of Us" research program uses the rich diversity in the general population to produce meaningful health outcomes research. There are also open communities that pool pharmacogenomic data and resources such as the Pharmacogene Variation Consortium (pharmvar.org), PharmGKB (pharmgkb.org), Pharmacogenomics Research Network (https://www.pgrn.org/), or the Clinical pharmacogenetics implantation consortium (cpicgx.org).

On top a patient's genetic profile, it is important to include metrics such as participant surveys, wearable technology data, food diaries, local environmental data, and repeat biosample screenings. The incorporation of psychosocial phenotypes such as catastrophizing (PCS), anxiety, depression, sleep disturbance, somatization, and social situation can also help elucidate causes behind health conditions. This, however, needs to be met with full patient participation, up-front data use policies, and proper encryption given the increasing privacy risks.

Pitfalls of Precision Medicine

While the field of personalized medicine has an exciting future, it also comes with its own challenges. To some the term itself can be misleading with somewhat arbitrary divisions. Much of the current studies only detect common variants. The relationship between genes and phenotype are not always clear as environment, exposures, and lifestyle can all influence genetic expression. Even within individuals with similar genetic and metabolic profiles, the pharmacokinetics and pharmacodynamics of medications can be variable especially considering other drug-drug interactions. Another criticism is that personalized medicine can focus on developing expensive treatments for small populations. Findings can be ambiguous and may find other genetic variants (Kiryluk et al. 2019). While the cost of genome

sequencing has gone down precipitously, it is still too cost and time prohibitive to perform point-of-care sequencing in the perioperative setting.

There are also a myriad of genes that can contribute to a single clinical metric such as the collection of genes associated with cardiac repolarization for people with long QT syndrome. With so many variants and expression profiles, it is difficult then to find individual statistical differences without clear a priori hypotheses given the statistical problem of multiple comparisons tests creating a large signal-to-noise problem.

In the two medical disciplines that represent the largest cause of morbidity—oncology and cardiology—personalized therapeutics has yet to show the hoped for salient changes in clinical outcomes. As the FDA is not able to approve use indication changes as fast as they can be detected, there are ethical issues around large scale off-label use of molecular targeting agents. The SHIVA trial compared the efficacy of molecularly targeted agents in advanced cancers, selecting patients with targetable mutations such as PI3K, AKT, mTOR, RAF/MEK with molecularly selective agents compared with conventional oncologic chemotherapy and did not show improvement in disease-free survival (Le Tourneau et al. 2015). As it stands, genome-informed therapies only help a minority of patients with advanced cancers, estimated around 7% (Marquart et al. 2018). However as our identification of new targets and therapies improve, likely so will our outcomes.

Within pain syndromes, there is an intimate, dependent relationship between the biological aspects of disease such as hyperexcitable nociceptor afferents and dysregulated neuronal circuitry with the patient's psychological state. Their experience of pain, then, is often holistically referred to using the biopsychosocial model. It is unclear how the biopsychosocial assessment will be leveraged.

Conclusion

Regional anesthesia has made large strides over the last few decades and the future stands to bring many more improvements and challenges. As our understanding of pharmacogenomics and large scale data science for interpreting clinical data improve, anesthesiologists will be able to use increasingly personalized methods for tailoring their anesthetic and within regional this can translate in many ways such as selecting the local anesthetic formulations, concentration, dose, site of injection for a specific duration, differential block, and adjuvants that would confer minimal toxicity and side effects while taking into account the patient's genetics, medical conditions, and medications.

It is conceivable that an integrated health record could indicate the best block concoction for a chosen anatomical location and duration, perhaps the site chosen based on imaging criteria of the nerve. New drugs will be developed including new local anesthetics, drugs that act on other areas of voltage-gated sodium channels, or drugs which act on other receptors such as TRPV1 in pain fibers.

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Chapter 15
Personalized Anesthesia for the Elderly

Ali Salehi

Introduction

The elderly population is growing globally due to decrease in mortality (advancements in medical treatment) and a parallel reduction in fertility rates (Lutz et al. 2008). For example in the United States the rate of population increase for people <65, 65–79 and >80 is 1, 2 and 3% respectively (Valvona and Sloan 1985). Among the elderly population in general and people above 80 years age in specific the ratio of female to male rises significantly since females live longer than males. With this picture in mind it is understandable that more elderly people will require surgical interventions and hence need perioperative anesthesia care. Factoring in that this patient population suffers from numerous comorbidities including but not limited to cardiovascular, renal, cerebrovascular, osteoarthritis and neurocognitive disorders, they pose a unique and immense challenge for the anesthesiologist. In order to provide optimal care for these patients, one needs to understand the personal variabilities in the pharmacokinetics/pharmacodynamics of drugs, frailty, baseline cognitive and activity levels in this population to be able to tailor an anesthetic plan that not only ensures a safe perioperative course but also returns the patient to the same level of activity and independence that they enjoyed prior to the procedure.

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Perioperative Care

Perioperative evaluation of elderly patients follows the same principles of any patient population which includes a thorough history and physical exam, relevant past medical, surgical and anesthetic history, allergies, functional status, current medications, laboratory/imaging findings and pre-procedure related preparation and optimization if necessary. There are certain population specific issues in the pre-operative period which play a significant role in the post-operative outcomes of the elderly patient population; which are discussed under 5 main subtitles here.

First is the concept of frailty. In evaluating elderly patients there could be a significant difference between an individual's chronological age and physiological age. There is a growing body of evidence that indicates that frail elderly experience poor outcomes that cannot be explained by age, functional status or comorbidities (Sadiq et al. 2018). One school of thought considers frailty a "Geriatric Syndrome" defined as a loss of function, decrease in physiological reserves, impaired stress response, and vulnerability to disease (Fried et al. 2001; Rockwood 2005; Bergman et al. 2007). Research has shown that frailty in the perioperative period is a valid indicator of postoperative complications including delirium, falls, discharge to skilled nursing facilities, readmissions (Boyd et al. 2005; Dasgupta et al. 2009; Makary et al. 2010; Pol et al. 2011; Schultz et al. 2015). Fried et al identified frailty as a biological condition (Fried et al. 2001). They defined the phenotype of frailty by 5 criteria:

1. unintentional weight loss >10 lbs over the past year
2. weak hand grip strength (measured by dynamometer)
3. self-reported exhaustion
4. slow gait speed
5. sedentary behavior

The severity of frailty is defined by number of criteria present (0 representing healthy, 1–2 prefrailty, ≥3 frailty).

Mitnitski et al. and Rockwood et al. (Rockwood et al. 2005; Rockwood and Mitnitski 2007) defined frailty as a sheer number of markers extracted from the patient's symptoms, signs, functional status, comorbidities and laboratory results and assess his/hers severity of illness or proximity to death. Both these approaches express frailty as a representative of deficits and each marker plays an equal role in assessing frailty. Numerous assessment tools have been developed but there is no consensus on the ideal tool for the perioperative period. One of the most useful tools is **Fried criteria**. Makary et al. (2010) showed using Fried Criteria as discussed above, frailty is associated with increased risk of postoperative complications, hospital length of stay and discharge to skilled nursing facility. Fried criteria can be done in short period of time but needs specific instruments (dynamometer). **Modified Frailty Index (MFI)** was developed by Velanovich et al.by choosing 11 variables from the original deficits frailty model (92 items) (Velanovich et al. 2013). These items include: activities of daily living, functional capacity, diabetes mellitus, COPD or pneumonia, myocardial infarction in past 6 months, previous

percutaneous coronary intervention or cardiac surgery or history of angina 1 month before surgery, congestive heart failure 30 days before surgery, hypertension that is currently being treated, impaired sensorium, cerebrovascular disease, and peripheral vascular disease or history of revascularization or amputation. The score for this index has a rage of 0–1 based on the number of criteria the patient meets (if the patient meets 6 items out of 11 or 6/11 his/her score is 0.54). MFI can be calculated based upon preexisting information from the patient's record but it is time consuming. A variation of MFI index has been used by other investigators to show it correlation with poor postoperative outcomes (Dindo et al. 2004; George et al. 2016). **First Minute Impression** was first proposed by O'Neill et al. (2016). The anesthesia provider has to answer the question "Is this patient fit for the proposed surgery" before obtaining history, performing physical exam, or reviewing laboratory results. This first impression is based on patient's independent mobility/gait, speed, balance, strength of hand shake, nutritional status and body habitus. If the answer to question is "not fit" patient is considered frail. This a very fast assessment but is not clearly validated. **Sarcopenia** aims to predict postoperative outcomes by using only the weakness criteria from the Fried's frailty tool. It is defined by cross sectional measurement of the rectus femoris muscle on ultrasound or the right and left psoas muscles at the level of L4 vertebra. Its validity and predictability has been verified in liver recipient patients and surgical ICU patients in comparison to a 50 item questionnaire based on the Canadian Study of Health and Aging (Joseph et al. 2014; Underwood et al. 2015; Mueller et al. 2016). The American College of Surgeons National Surgical Quality Improvement Program (NSQUIP) and the American Geriatrics Society (AGS) strongly recommend that elderly patients undergoing surgical procedures to be assessed for frailty syndrome and its severity documented in the patient's medical record (Chow et al. 2012). This can lead to a more patient centric care plan and make the goals and expectations of the procedure clearer for both the patient and care provider (Robinson et al. 2015) and enable the surgical/anesthesia teams to incorporate addressing patient's goals and risks as part of standard patient care (Mohanty et al. 2016; Shem Tov and Matot 2017). It should be noted that the method of assessment of frailty should differ in different preoperative settings. For example a 50 variable Rockwood frailty index may be a feasible tool in the perioperative clinic but is not appropriate in same day surgery or emergency surgery setting. Furthermore the diversity in the assessment tools should not prevent the anesthesiologist from assessing frailty since using one tool is better than eliminating it all together (Forman and Alexander 2016). The next question facing us is that whether any perioperative interventions can be used to target frailty. Prehabilitation as a method to evaluate preoperative physical and mental status and improving them through appropriate interventions in order to enhance postoperative outcomes and return the patients to their maximal functional capacity is the main stay of this effort (Hulzebos and van Meeteren 2016; Shem Tov and Matot 2017). Lee et al. in an observational study of 132 nondemented English speaking elderly patients undergoing elective orthopedic surgery showed that regular physical activity (PA) (6–7 times per week) decreased the odd ratio of postoperative delirium by 73% (Lee et al. 2019). Their findings were in line with previous reports of the role

of PA in reducing the risk of delirium in hospitalized patients (Yang et al. 2008). They noted that a fair amount of physical activity is needed to observe a meaningful effect on postoperative risk of delirium. They also demonstrated that the benefit of PA is independent of the baseline cognitive reserve and status in their nondemented cohort. It is important to note that PA may not be possible in patients with joint disease or may have inherent risk due to their underlying comorbidities.

Second concept is preoperative neurocognitive assessment and informed consent. This is of utmost importance not only because preoperative cognitive impairment is a risk factor for perioperative neurocognitive disorder (PND) and postoperative delirium (Greene et al. 2009; Silbert et al. 2015) but it also underlines the fact that the patient should be able to receive, understand, ask relevant questions and offer informed consent regarding their medical care (Berger et al. 2018). We assess other organ systems through history, physical exam and laboratory studies. Since central nervous system (CNS) is the target of all our anesthetic agents and CNS impairment is a major risk factor for PND it makes it clear that an evaluation of baseline CNS function is relevant (Berger et al. 2015). This also allows for risk stratification of patients for PND and allocating resources and utilization of perioperative protocols to prevent PND including sleep and nutrition improvement, avoidance of specific medications, rapid return of glasses and hearing aids postoperatively and early family engagement (Chan et al. 2013). Identifying patients with mild cognitive impairment who are at increased risk of PND will also allow discussions about postoperative expectations and will enable the patients and their families to make important life decisions before or weeks to months after surgery (Berger et al. 2018). In regards to what type of assessment tools to use, it is impractical and infeasible to use lengthy neuropsychological tools in the perioperative setting in contrast to brief cognitive screening tests. There is no sufficient evidence to support which of the brief screening tests available have a more powerful predictability and usefulness in the perioperative period. Some of the recommended brief cognitive tools include Mini Mental State Examination (MMSE), Montreal Cognitive assessment (MoCA), Mini-Cog, Clock drawing test, Cognitive Disorder Examination (CODEX). MMSE is widely used and studied with 88% sensitivity and 86% specificity and it takes 7–10 min to administer (Kazmierski et al. 2006; Lin et al. 2013). MoCA can identify mild cognitive impairment and is available in multiple languages (Aykut et al. 2013; Partridge et al. 2014). Mini-Cog is brief with minimal language, education and race bias (Culley et al. 2016; Dworkin et al. 2016). It has 76–100% sensitivity and 54–85% specificity and takes 2–4 min to administer.

The other area of research to identify patients at risk of cognitive decline are the inflammatory biomarkers IL-6, TNF-α and C-reactive protein. It has been shown that patients with a higher circulating levels of IL-6 are at increased risk of cognitive decline in a 2–7 year follow-up period (Bradburn et al. 2017). Since both anesthetic and surgical factors contribute to PND and there is a growing trend toward multidisciplinary approach toward the care of elderly patients it is imperative that both anesthesiologists and surgeons discuss PND risks through consent process (Glance et al. 2014; Terrando et al. 2015; Berger et al. 2018). The challenge in this process is that most often the patients see their surgeon or anesthesiologist at the day of surgery

just minutes to hours prior to the procedure instead of days ahead in order to able to process the information, ask questions and make necessary decisions.

Third concept is polypharmacy and the elderly. The elderly patient population as mentioned before has a higher burden of comorbidities and hence is taking multiple medications both prescribed and over the counter (Qato et al. 2008). Polypharmacy is referred to as taking 5 or more medications at the same time and is associated with increased risk of adverse drug events and hospitalization (Juurlink et al. 2003). Polypharmacy can be seen in any patient population but is more common in the elderly. It has been shown that 90% of people ≥65 years of age are on at least 1 medication, 40% on 5 medication and 14–19% on 10 medication per week (Qato et al. 2008). Furthermore 42% took over the counter meds and 52% took dietary supplements (Glance et al. 2014). The most common family of drugs prescribed is the cardiovascular agents. This illustrates the fact that the anesthesiologist should review all medications and be aware of the most common drug interactions (Barnett 2009). Drug related adverse events are a major factor in health care costs due hospital admissions and increase mortality and morbidity. Elderly perioperative medications should be reviewed and reconciled preferably by a pharmacist which can help reduce errors (van den Bemt et al. 2009). Electronic medical records also play a major role in eliminating the discrepancies that can exist between the surgical, anesthesiology and nursing services in regard to the patient's medications. Burda et al. in a small prospective study looking at the concordance between anesthesia and surgical medication lists of admitted patients found a 53% discrepancy in at least one medication, 23% had different allergies, 56% had different perioperative medication list and 43% had different dosing and frequency recommendations. It may be prudent that elderly patients bring all their meds or a complete list to their perioperative visit (Burda et al. 2005).

Another hurdle regarding polypharmacy is medication adherence. Elderly patients may have an issue in following the correct instructions for their medications. Factors that contribute to non-adherence are old age, drug costs and side effects, dosing more than once a day, multiple medications, and complex schedules. In order to improve perioperative drug adherence it is prudent to handout written instructions (Barnett 2009). The next step is to identify inappropriate drugs (risk of adverse effects outweighs its benefits) in the patient's list. Beers developed a set of criteria known as **Beers criteria** to identify inappropriate medication prescription (Beers 1997). It has undergone several revisions over the years. The most notable inappropriate drug categories in the perioperative period as identified by Beers criteria include (Aparasu and Mort 2000; Jano and Aparasu 2007).

1. medications with significant anticholinergic activity like diphenhydramine, hydroxyzine, and promethazine
2. long acting benzodiazepines like diazepam and flurazepam

Polypharmacy is not limited to prescription medications but also involves over the counter (OTC) medications as well. These include vitamins and supplements. We have limited information regarding their effect on anesthetic agents. American Society of Anesthesiologists recommends that all herbal and

non-herbal supplements to be stopped 2 weeks prior surgery when appropriate. Chondroitin and glucosamine are one of the most common supplements used by the elderly population. They are presumed safe but evidence is limited (Ang-Lee et al. 2001; Qato et al. 2008). Among the herbal supplements Ginkgo and garlic are among the most frequently used OTCs. Ginkgo which is derived from Ginkgo biloba is perceived to improve memory and cognition but has been associated with bleeding complications in the perioperative period. Garlic possess several active ingredients like alliin, allicin and ajoene that help improve cardiovascular health (Qato et al. 2008). Garlic also inhibits platelet aggregation and potentiate other platelet inhibitors resulting in bleeding. These herbal supplements may potentially cause drug-drug interaction with anticoagulants (Ang-Lee et al. 2001). In the aging population neuropsychiatric (depression, dementia, Alzheimer's disease and Parkinson's disease) and cardiovascular disorders are the 2 most prevalent and the drugs used for treatment are of utmost importance in causing drug-drug interaction. Monoamine oxidase inhibitors (MAOIs) are used to treat severe depression. They prevent the metabolism and breakdown of norepinephrine and serotonin which results in an increase in the available level of these neurotransmitters. Drugs like phenelzine (Nardil) and Tranylcypromine (Parnate) are nonselective inhibitors of MAOI inhibiting both MAOI type A & B. This inhibition last for 30 days and it takes 14 days to produce adequate levels of active enzyme (Barnett 2009). Exaggerated hypertensive responses to administration of indirect acting sympathomimetic agents (i.e. ephedrine) is seen in patients on MAOIs. It is recommended to treat hypotension with direct acting agents i.e. phenylephrine. Drugs like meperidine, selective serotonin reuptake inhibitors (SSRIs) if concurrently used with a MAOI can lead to rapid accumulation of serotonin and serotonin crisis which manifests as headaches, agitation, delirium, convulsions and hyperthermia and can be fatal (Huyse et al. 2006; Hayes et al. 2007). SSRIs such as fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), citalopram (Celexa) and escitalopram (Lexapro) are wildly used in the elderly population to treat depression and obsessive compulsive disorders because they lack anticholinergic effects. Duloxetine (Cymbalta) is a selective SSRI and norepinephrine reuptake inhibitor used to treat major depression and diabetic neuropathy (Huyse et al. 2006). Anti-Parkinson medications like Levodopa despite their short half-life can have different side effects including hypotension and hypovolemia. Anti-dopaminergic drugs like metoclopramide, phenothiazine like prochlorperazine (Compazine) that are used as antiemetics should be avoided in this patient population due to the risk of worsening the symptoms of Parkinson's disease (Huyse et al. 2006; Hayes et al. 2007). Acetylcholinesterase inhibitors that are used in the treatment of Alzheimer's disease such as donepezil and rivastigmine can interfere with the metabolism of cholinesterase dependent muscle relaxants and there are reports of prolonged paralysis with succinylcholine (Fodale et al. 2006; Jones and Soderman 2007). It is a wide consensus that all cardiovascular medications which can include beta blockers, calcium channel blockers and ACE

inhibitors/Angiotensin receptor blockers (ARBs) be continued through the perioperative period. The use of ACE inhibitors and ARBs can lead to refractory and difficult to treat hypotension in the perioperative period (Augoustides 2008; Kheterpal et al. 2008). It is preferred that there should be a gap of at least 10 h between taking these medication and time of surgery.

Fourth is nutritional status and preoperative fasting. The prevalence of malnutrition is about 45–55% based on different reports (Pirlich et al. 2006; Konturek et al. 2015). Malnutrition is associated with increased risk of postoperative complications including wound healing and postoperative delirium (Phillips 1986). Elderly patients should have a nutritional assessment and their nutritional intake optimized if possible during their preoperative evaluation. Mini Nutritional Assessment (MNA-SF) and Nutritional Risk Screening (NRS2000) are among the screening tools available (Kondrup et al. 2003; Kaiser et al. 2009). MNA-SF is suitable for both in an outpatient settings and NRS2000 is more for inpatient evaluation. Elderly patients do not tolerate dehydration well. It may cause anxiety and agitation and facilitate postoperative delirium (POD) (Radtke et al. 2010). Patients can be fasting for 6 h for prevention and reduction of the risk of aspiration. Elderly patients should be able to drink clear liquids up to 2 h prior the procedure and access to carbohydrate containing drinks up to 2 h before the surgery can have a beneficial effect on the well-being of the patient (Smith et al. 2014; Amer et al. 2017).

Fifth is the assessment of cardiovascular disease in the elderly. Cardiovascular disease (CAD) is common in the elderly and they suffer a higher rate of adverse cardiovascular events (Goff et al. 2014). The standard evaluation tools consists of electrocardiography, echocardiography, stress testing, and coronary angiography. The elderly patient population is higher risk of procedure related complications during their evaluation process (Ahmed et al. 2009). This increased risk indicates that the elderly may benefit more from a timely determination of their CAD risk. This risk is even heightened since the elderly show atypical signs and symptoms of CAD. Ladapo et al. used a quantitative blood-based precision medicine test that incorporated age, sex, and gene expression score into an algorithmic scale (ASGES) which was developed to assess the current likelihood of obstructive CAD, defined as at least one atherosclerotic plaque causing 50% or more luminal diameter stenosis in a major coronary artery ($\geq$1.5-mm lumen diameter) to examine its clinical utility and its effects on medical decision-making, with an emphasis on referrals to cardiology or advanced cardiac testing. They demonstrated that elderly with higher scores had a higher rate of referral for cardiology and cardiovascular testing and also had a higher incidence rate of major adverse cardiac events and revascularization rates at 1 year follow-up. ASGES may be an alternative for conventional stress testing for the elderly since it can be done during an office visit without the need for referral to a specialized testing center and the physical limitations of the elderly to achieve optimal exercise level during a stress test (Ladapo et al. 2018).

Intraoperative Care

In order to tailor a personalized intraoperative anesthetic plan we should understand the physiological changes and pharmacokinetics and pharmacodynamics of commonly used anesthetics in the elderly. This enables the anesthesiologist to choose the appropriate anesthetic technique and drug selection and dosages for premedication, maintenance and emergence of anesthesia which can lead to enhanced recovery and return to baseline functional class and reduction of anesthetic related complications. This is in addition to the procedure specific considerations regarding positioning, monitoring and hemodynamic management.

Age related physiological changes can be categorized by organ systems:

1. Cardiovascular: Aging is associated with a reduction in aortic and greater vessels elasticity and compliance (Vaitkevicius et al. 1993). This leads to a higher systolic blood pressure, increased afterload resulting in left ventricular hypertrophy and fibrosis (Chen et al. 1998). This in return will impair myocardial relaxation during diastole (diastolic dysfunction) and decrease passive filling of the LV and increased reliance on atrial kick for maintenance of adequate stroke volume (Geokas et al. 1990). The other major change is the reduction of intrinsic heart rate and prolongation of sinoatrial conduction time which leads to a change in maintenance of cardiac output (CO) between the young and the elderly (Josephson 1999, 2004, 2007; Katritsis et al. 2017). In young individuals CO is maintained by increasing heart rate in contrast to the elderly which maintain CO by increasing stroke volume (Lakatta and Levy 2003). Gradually this capability is also reduced resulting in a reduction in aerobic capacity.
2. Renal: Renal mass decreases with age, which reflects the decrease in the number of nephrons in the process of aging along with hyalinization of the vascular tufts leading to decrease in the blood flow in the afferent arterioles (McLachlan 1978; Tracy et al. 2002). There is no change in the medullary vasculature (Ljungqvist and Lagergren 1962). The rate of age related loss of renal parenchyma is 10% per decade of age increase (Gourtsoyiannis et al. 1990). These overall changes reduce renal blood flow and glomerular filtration rate but there is no change in creatinine clearance due to concomitant loss of muscle mass (Davies and Shock 1950; Lindeman et al. 1985). Therefore GFR is a more reliable marker that plasma creatinine to assess kidney function. There is also telomere shortening and a decrease expression of the klotho antiaging gene which enhances tubular atrophy and reduction in organic acid, proton and potassium clearance (Zhou et al. 2008).
3. Liver: Liver mass and blood flow decreases with aging (Koff et al. 1973). This change affects phase 1 catalysis by cytochrome P450 enzymes than phase II conjugation. This effects both total drug clearance and free drug clearance (McLean and Le Couteur 2004; Ginsberg et al. 2005). Protein synthesis does not show any changes in healthy elderly patient between ages 50–69 and 70–89.
4. Respiratory: Vital capacity and total lung capacity decrease during aging while functional residual capacity (FRC) and closing volume increase which can result

in the collapse of smaller airways and air trapping (Wahba 1983). There is also a reduction in the arterial oxygen tension and ventilator response to hypercapnia and acidosis contributing to an increased risk for perioperative respiratory complications (Cope and Hunter 2003).

5. GI tract: Gastric emptying remains unchanged in the elderly while hydrochloric acid and pepsin production is decreased (Gainsborough et al. 1993; Blechman and Gelb 1999). Small intestine motility and digestion remains unchanged while there is a reduction in the absorption of Ca, sugar and iron (Husebye and Engedal 1992).
6. Musculoskeletal and whole body: Muscle mass and total body water are reduced which results in a smaller volume of distribution for hydrophilic drugs (Fulop et al. 1985). Conversely total body fat increases by 20–40% which increases the volume of distribution for lipophilic drugs (McLean and Le Couteur 2004; Ginsberg et al. 2005). Elderly patients also have impaired thermoregulation predisposing them to hypothermia which could lead prolonged duration of action of certain anesthetic medications.

Pharmacokinetics in the Elderly The 3 major aspects of pharmacokinetics of a drug is its volume of distribution (V^d), clearance (Cl) and elimination half-life (t1/2). Hydrophilic medications like most non-depolarizing muscle relaxants have a smaller v^d due to decrease in total body water in the elderly leading to higher plasma concentrations, but since they are mostly secreted through the kidneys and since the renal blood flow and subsequently their Cl has decreased the net effect on their elimination half-life is neutral and their t1/2 is unchanged ($T1/2 = 0.693 \times Vd/Cl$) (Vestal et al. 1977). So these medication require a smaller induction doses. Lipophilic medication like benzodiazepines, barbiturates, propofol have a larger V^d due to increase in body fat during aging process hence they have a longer t1/2 (Greenblatt et al. 1980; Christensen et al. 1981). Protein binding is another factor that can affect plasma levels of free medications. Acidic drugs (benzodiazepines, warfarin…) who are negatively charge primarily bind to albumin which is a positively charged protein where as basic drugs bind to α1-acid glycoprotein. Plasma albumin levels are decreased in acute illness and malnourished patients where as α1-acid glycoprotein levels are increased in acute illness (Mangoni and Jackson 2004). Although changes in the plasma levels of these proteins may have a potential role in drug interactions for highly protein bound drugs, their clinical relevance is limited due to the balancing effect of the clearance of these free drugs (Benet and Hoener 2002). Renal clearance of medications is assumed to be decreased due to decrease in the number of nephrons and renal blood flow. Some studies suggest that despite this reduction the renal clearance in elderly similar to young adults (Fliser et al. 1999). Clearance of medications by the liver depends on the blood flow to the liver and the extraction ratio of the drug by the liver.

$$Cl = E = Q \times \frac{C^a - C^V}{C^a}$$

Which Cl is liver clearance, Q = liver blood flow, C^a = drug concentration in hepatic artery or portal vein, C^v = drug concentration in hepatic artery and E is steady state extraction ratio. Medications are categorized in 3 groups based upon their E: high E > 0.7 like propranolol, medium E 0.3–0.7 like codeine, morphine and aspirin and Low E < 0.3 like diazepam and phenytoin (Mangoni and Jackson 2004). When the E for a drug is high the rate limiting factor for clearance is hepatic blood flow, but when the E is low the concentration of the drug in the hepatic artery/portal vein is close to the drug concentration in hepatic vein and changes in hepatic blood flow have little effect on clearance. So aging only affects the clearance of drugs with high extraction ratio. It has been shown in some studies that a reduction in renal function may also effect the clearance of medications that undergo high metabolism in the liver (Yuan and Venitz 2000). A reduction in activity of cytochrome P450 due to decreased gene expression has been observed in patients with reduced renal function (Pichette and Leblond 2003).

Pharmacodynamics in the Elderly Dose adjustment and age related drug reactions are the 2 most pressing issues regarding pharmacodynamics in the elderly. The minimum alveolar concentration (MAC) of volatile anesthetics reduces by 6% for every decade of life after 30 years of age (Eger 2001). Since the therapeutic index of volatile anesthetics is narrow (Fast et al. 2008), it is of utmost importance to closely monitor and use the age adjusted MAC fraction of these agents in the elderly to avoid overdose and possible side effects including hemodynamic instability and postoperative delirium (Apfel et al. 2002; Radtke et al. 2013).

In the CODA study a 39% reduction in the dose adjusted end-tidal MAC resulted in a 35% decrease in postoperative delirium and 31% reduction of postoperative cognitive dysfunction at 3 months (Chan et al. 2013). It seems that regional anesthesia techniques and peripheral nerve blocks use as an adjunct or free standing technique to replace general anesthesia should decrease the prevalence of PND, but current evidence does not support it (Guay 2011; Silbert et al. 2014). However in most of the studies patients receiving regional anesthesia also received intravenous sedation.

Studies looking at other intravenous anesthetics to maintain general anesthesia and reduce PND did not produce any consensus results (Silbert et al. 2006; Hudetz et al. 2009; Su et al. 2016; Avidan et al. 2017; Deiner et al. 2017). Bispectral Index (BIS) or processed EEG monitoring can help to titrate anesthetic depth and reduce PND, but the studies evaluating their results yielded mixed results (Farag et al. 2006; Chan et al. 2013; Radtke et al. 2013). There is a linear relationship between the age adjusted MAC and the BIS values over the clinically acceptable range of volatile anesthetics (0.5–1.5 MAC) (Ni et al. 2019). This relationship is suggestive of the fact that especially in the elderly group of patients titrating volatile anesthetics to BIS values is more difficult than anticipated and also may result in patient receiving higher than desired anesthetic doses (Whitlock et al. 2011). There are ongoing studies that will probably provide guidance on the usage of raw EEG to titrate anesthesia depth and reduce PND (Wildes et al. 2016, 2019; Cui et al. 2017; Aranake-Chrisinger et al. 2018). There is consensus that EEG parameters should be used to guide the titration of depth of anesthesia in the elderly (Berger et al. 2015, 2018).

The other parameter to consider in a personalized anesthesia technique for the elderly is the blood pressure. Hypotension defined based on the patient's baseline blood pressure parameters (a drop >25% from baseline) should be avoided to sustain adequate end organ perfusion. This is important because incidence of hypertension is high among the elderly and it shifts the cerebral and end organ autoregulation curve to the right and if the blood pressure goals are defined based on historical population cutoffs instead of personal baseline parameters it could lead to end organ injury. The consensus guideline for intraoperative management of the elderly is summarized in Table 15.1 (Berger et al. 2018). There is no consensus on which anesthetic technique is superior for the elderly but there is consensus on which medications should be avoided or used with caution in this patient population (Table 15.2) (Berger et al. 2018).

Table 15.1 Intraoperative guidelines to improve postoperative outcomes in the elderly

1.	Avoid centrally acting medications like anticholinergics, benzodiazepines and meperidine.
2.	Avoid relative hypotension
3.	Maintain normothermia
4.	Monitor age adjusted end-tidal MAC
5.	Use EEG based brain monitoring to titrate anesthetic depth

From: Berger M, Schenning KJ, Brown CH, et al. Best practices for postoperative brain health: Recommendations from the fifth international perioperative neurotoxicity working group. Anesth Analg 2018; 127:1406–13 (31)

Table 15.2 Medications to avoid or use with caution in the elderly

Medication or class	Example	Rational
First generation anti histamines	Diphenhydramine	Central anticholinergic effects
Phenothiazine type antiemetics	Promethazine, prochlorperazine	Central anticholinergic effects
Antispasmodics/ anticholinergics	Atropine, scopolamine	Central anticholinergic effects
Antipsychotics (first and second generation)	Haloperidol	Risk of tardive dyskinesia, neuroleptic malignant syndrome, cognitive dysfunction and delirium
Benzodiazepines	Midazolam, diazepam	Cognitive impairment, delirium
Corticosteroids	Hydrocortisone. Methylprednisolone	Cognitive impairment, delirium and psychosis
H2 receptor agonists	Ranitidine	Cognitive impairment, delirium
Metoclopramide		Extrapyramidal effects
Meperidine		Neurotoxic effects
Skeletal muscle relaxants	Cyclobenzaprine	Anticholinergic effects

From: Berger M, Schenning KJ, Brown CH, et al. Best practices for postoperative brain health: Recommendations from the fifth international perioperative neurotoxicity working group. Anesth Analg 2018; 127:1406–13 (31)

Postoperative Care

Postoperative care of the elderly involves several factors specific to this patient population. First is identification and prevention of postoperative delirium. There are several validated tools for assessment of postoperative delirium (POD) including Confusion assessment Method for the Intensive Care (CAM-ICU), Intensive Care Screening Checklist (ICDSC), and Delirium Observation Screening Scale (DOS) (Olotu et al. 2019). Screening for delirium should start from immediate postoperative phase up to postoperative day 5 (Aldecoa et al. 2017). Prevention of delirium consists of pharmacologic and non-pharmacologic approach. Non-pharmacological approach include the following steps (National Clinical Guideline 2010):

- Orientation and early return of hearing and visual aids
- Stimulation and communication
- Early Mobilization
- Regulation of the sleep-awake cycle
- Early involvement of relatives and person of trust

Pharmacologic approach is selection and adjustment of doses of medications and the use of adjunct methods of intraoperative and postoperative pain management which we will discuss in more detail. The first step in postoperative pain management is assessment of the severity of pain. This consists of assessing pain right after the procedure, when the characteristics of the pain has changed or relief is inadequate. It is also important to assess dynamic pain relief, patient's ability to move or cough without pain, as an indicator of optimal pain relief (National Clinical Guideline 2010; Falzone et al. 2013). For non-demented elderly there are several self-reporting pain scales. These scales require the individual to understand the directions and communicate in response to the pain they are experiencing. These scales consists visual analogue scale (VAS), Verbal rating scale (VRS) which uses the terms none, mild, moderate and severe to describe the pain and Numeric rating scale (NPS) from 0 = no pain to 10 = worst pain in the perioperative period VRS and NRS are more reliable and validated and more favored by patients (Gagliese and Katz 2003; Gagliese and Melzack 2003; Gagliese 2009). In older patients with mild to moderate cognitive dysfunction VRS is still an acceptable tool but requires repeated explanations and more time to ensure optimal response (Coldrey et al. 2011). In patients suffering from severe cognitive dysfunction or postoperative delirium (POD) behavioral assessment tools are utilized; "Doloplus" and "Doloplus-2" scales are validated for elderly patients but they are time consuming to apply (Zwakhalen et al. 2006; Torvik et al. 2010). Algoplus is another validated tool in this group of patient which can be applied in a shorter time (Rat et al. 2011). It is comprised of the following elements:

- Face: frowning, grimacing, clenching, frozen face
- Look: inattentive gaze, fixed or distant begging, crying, eyes closed
- Complaints: "ouch" it hurts, moans, cries
- Body: removal or protection of an area, refusal and fixed attitudes
- Behavior: aggression, grabbing

Observance of one behavior in a category counts as a yes and earns 1 point. A score ≥ 2/5 is a sign of pain.

The next step is administration of pain medications which should be selected and dose adjusted based upon the physiologic changes in the elderly and the pharmacokinetic and pharmacodynamic changes that occur due to advanced age.

Non-opioid Medications

1. Acetaminophen: It is a centrally acting prostaglandin inhibitor which has limited side effects. Its most serious side effect is dose dependent hepatic necrosis due to acute over dose. It is well tolerated and there is no need to adjust its dose in the elderly unless significant renal dysfunction exists (Coldrey et al. 2011; Liukas et al. 2011).
2. Nonsteroidal anti-inflammatory drugs (NSAIDs): They inhibit prostaglandin production both centrally and peripherally through the inhibition of cyclooxygenase 1 and 2 (COX1 & COX2) isoenzymes. Non selective NSAIDs like ketorolac and diclofenac augment pain relief with a strong analgesic effect while reducing opioid requirements and thus reducing opioid associated side effects. Main concern is their adverse effects in the elderly patients which include cardiovascular (CV), gastrointestinal (GI) and renal (Barkin et al. 2010; Coldrey et al. 2011). Their short term use appears to be safe in regards to CVS events. Risk of renal injury is higher in elderly patients who have baseline renal dysfunction, heart failure or taking other nephrotoxic agents. It is recommended that their dose to be decreased by 25–50% with an increased in their dose interval (Aubrun and Marmion 2007) and if GFR is <50 ml/min they should be avoided. GI bleed associated with the use of NSAIDs is 2× as high in patients >65 years old.

Opioids

Opioids are the mainstay of postoperative pain management. They can be administered orally, intravenous boluses, continuous fusion (patient controlled analgesia PCA), epidural infusion (patient controlled epidural analgesia PCEA). The doses of opioids should be reduced irrespective of the route used due to the relative effect of aging on physiology and pharmacokinetic and dynamic of these drugs. A "start low, go slow" approach is appropriate due to the increase elimination half-life of these drugs

1. Tramadol: It is atypical centrally acting agent binding to the μ-opioid receptor and inhibiting serotonin and norepinephrine re-uptake with less respiratory depression than morphine. It is ¼ as potent as morphine. The daily dose of Tramadol is 400 mg/day and its active metabolite O-desmethyltramadol is more potent than tramadol. It is metabolized in the liver and excreted through the kid-

ney and hence its Cl is decreased and its elimination half-life is increased in patients with liver and renal dysfunction there its dose needs to be decreased (Coldrey et al. 2011). Tramadol should be used with caution in patients with history of seizures or on anti-seizure medications and be avoided in patients using MAOIs or SSRIs (Jick et al. 1998).

2. Codeine: It is a natural alkaloid in opium that has less affinity to the μ-receptor than morphine. It is a pro-drug metabolized in the liver via P4502D6 to morphine. P4502D6 is prone to drug interaction with common drugs used by the elderly (fluoxetine, cimetidine) and is totally absent in 8% of the population which renders codeine ineffective in this group of patients (Falzone et al. 2013). This produces a large variance in effectiveness among elderly patients. The dose should be halved in the elderly in comparison to young patients and the intervals should be increased (Aubrun and Marmion 2007). It has the same adverse effect profile as morphine (nausea/vomiting, constipation, itching and cognitive impairment).
3. Morphine: It is the most commonly used opioid for postoperative pain control. Its aged related pharmacokinetic and pharmacodynamics changes include (Aubrun and Marmion 2007; Coldrey et al. 2011):

- ↑ mean elimination half life
- ↓ decrease volume of distribution
- ↓ Clearance
- ↓ protein binding
- ↑ brain sensitivity

Morphine's metabolite morphine-6 glucuronide which is more potent than morphine can accumulate in patients with renal impairment. This will increase the incidence of morphine related adverse effects (Chauvin et al. 1987; Dean 2004; Sverrisdottir et al. 2015). Respiratory depression is one of the most side effects of morphine especially in patients with ↓ renal function necessitating monitoring of sedation as the best indicator and warning sign of respiratory depression. Supplemental O2 is recommended for the first 48–72 h after surgery (Macintyre and Jarvis 1996; Semple et al. 1997; Ludbrook et al. 2001; Lim and Macintyre 2006; Pergolizzi et al. 2008; Krishnamurthy et al. 2012; Macintyre et al. 2013). For all the reason's mentioned the dose of morphine should be decreased 30–50% in the elderly, but it can be increased if analgesia inadequate (Burns et al. 1989; Macintyre and Jarvis 1996; Coldrey et al. 2011). Different modes of opioid use includes but not limited to the following:

- Intermittent boluses: morphine is used as intermittent boluses the usual dose is 2–3 mg every 5 min (Aubrun et al. 2002). In patients >65 years old 2 mg is an appropriate dose with the same analgesic profile as young patients with no increased risk of sedation (Keita et al. 2008). In patients >90 years old if morphine is considered the dose should be decreased to 1 mg and intervals increased (Aubrun et al. 2002).

- Subcutaneous administration: subcutaneous morphine should be avoided due to variability of absorption rate and variance in drug effect and the risk of adverse effects 30–60 min after administration (Capdevila et al. 1998; Falzone et al. 2013).
- Patient controlled analgesia: PCA is as effective in elderly patients as leads to better patient satisfaction than intermittent boluses (Macintyre and Jarvis 1996; Keita et al. 2003). A prospective study of patients >70 years old showed that 24% of the patients did not have the cognitive capability to use PCA (Mann et al. 2000). Morphine is the preferred drug in PCA and with a 1 mg every 5–10 min with a maximum hourly dose set. Continuous back ground infusion should be avoided due to increased risk of respiratory depression (Falzone et al. 2013).
- Epidural analgesia: epidural analgesia is superior to other modes of pain management (Macintyre and Jarvis 1996; Macintyre et al. 2013; Schug et al. 2016), but its potential risks versus benefits in elderly population should be considered as it can potentially delay mobility and rehabilitation. During aging process there is a progressive occlusion of the intervertebral foramina which limits the spread of the epidural space. This leads to a more extensive spread of the local anesthetics (LAs) which implies a smaller volume of LAs are needed in comparison to younger patients (Sharrock 1978). The concentration necessary to achieve effective motor blockade also decreases with age (Svircevic et al. 2011). It is recommended an opioid be used along with the local anesthetic (LA) to reduce the risk of LA associated hypotension and motor blockade and it also helps to decrease the risk of respiratory depression by the opioid agent as well (Liu et al. 1995). Patients should be on supplemental O2 and be monitored every 2–4 h (Olotu et al. 2019).
- Patient controlled epidural analgesia (PCEA): PCEA is associated with decreased LA consumption and LA associated adverse events (Silvasti and Pitkanen 2001). Although there is no standard protocol for the use of PCEA in elderly patients it is recommended to use a combination of LA and opioids for the reasons mentioned before with a back ground infusion rate of 3–6 cc/h and a bolus of 2–3 cc every 15–20 min (Wigfull and Welchew 2001).

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Chapter 16
The Role of Artificial Intelligence in Personalized Anesthesiology and Perioperative Medicine

Richard Boyer and Lei Gao

Introduction

The practice of anesthesiology has evolved over the last two decades from a field focused on the intraoperative and postoperative phases of care, to now encompass an entire perioperative medicine specialty with the goal of continuous optimization of patients from preoperative risk reduction to postoperative recovery and prevention. This transition from a largely reactive to a proactive and preventative perioperative specialty has opened the door to new opportunities for personalized medicine, particularly by leveraging the vast amounts of data generated today in our electronic health record systems, interconnected medical devices and consumer wearables. It is estimated that over 2000 exabytes (1 exabyte = 1 billion gigabytes) of healthcare data will be generated in 2020 (Dimitrov 2016; Ibarra-Esquer et al. 2017; Sheth et al. 2018). Clearly, analyzing all of the available healthcare data today for informed clinical decision-making is beyond the ability of any single clinician. Data science and artificial intelligence are therefore playing increasingly important roles in today's healthcare system, and particularly in the data-intensive field of anesthesiology.

Data science is a rapidly evolving interdisciplinary field of applied mathematics, statistics and computer science that extracts knowledge from increasingly large and

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complex datasets. Artificial intelligence, although often discussed interchangeably with data science, is specifically focused on computer systems which are capable of solving problems that traditionally require human intelligence. Machine learning and deep learning are computational techniques at the intersection of data science and artificial intelligence that are often employed in large healthcare datasets where standard logistic regression and statistical methods are inefficient or impractical. Machine learning uses algorithms such as decision trees, vector machines or Bayesian learning to achieve weak artificial intelligence, while deep learning uses higher-order neural networks and similar algorithms to achieve higher artificial intelligence.

In healthcare, high-volume information assets are ubiquitous, with countless patient records existing in tens of thousands of disparate electronic health record systems. We think of healthcare data in terms of two major buckets—big data (large N to create population level models and hypotheses) and small data (small N or N = 1 to create individual models and hypotheses) (Ofili et al. 2018; Hekler et al. 2019). In healthcare, big data often refers to electronic health records, genetic data, billing records and clinical research data, while small data often includes patient monitor data and patient generated health data from consumer health devices, wearables and mobile applications. While big data practitioners aim to process this vast patient data to model the generalized population and apply systematic hypotheses to individuals, small data practitioners, conversely, use individual digital phenotypes (aka "digital fingerprints") and subject-specific data to inform algorithms and develop individualized models. In simpler terms, while the strength of big data is evidence-based medicine, or applying population-based hypothesis to a patient, the strength of small data is precision or personalized medicine through modeling of the individual.

Murdoch and Detsky theorized in their 2013 JAMA article "The Inevitable Application of Big Data to Health Care" that big data would advance medicine in four main areas: generation of new medical knowledge, dissemination of medical knowledge, translation of personalized medicine initiatives into clinical practice and empowerment of patients with actionable data (Murdoch and Detsky 2013). For the most part, Murdoch and Detsky have been proven right. Advancement of machine learning, deep learning and natural language processing in electronic health records, using tools such as IBM Watson, have increased our medical knowledge base. Clinical decision support tools that integrate AI techniques have also been developed to apply patient data analytics to evidence-based clinical guidelines. However, unlike medical oncology, which has heavily invested in genomics and precision medicine initiatives, anesthesiology and perioperative medicine have lagged behind in the implementation of personalized anesthesiology and perioperative big data technologies.

In the preoperative assessment, anesthesiologists often describe an individual based on a risk stratification score, such as American Society of Anesthesiologists (ASA) class 1–6 or the Revised Cardiac Risk Index (RCRI). While these classifiers are helpful for high-level preoperative risk stratification, in order to personalize a patient's perioperative plan, additional data is needed to understand their specific

medical comorbidities, functional capacity, hemodynamic status, nutritional status and mental fitness. Advancements in big data and small data mining and analysis are assisting us in supplementing our existing risk classifiers with the data produced by electronic health records, physiologic monitors, consumer health devices and smartphones for perioperative management. High fidelity patient waveform recordings and machine learning algorithms have also introduced a new dimension to patient analytics, with millisecond-resolution data that allow us to model dynamical physiology and real-time hemodynamic status (Cannesson et al. 2019). Additionally, wearable monitors are producing prehospital patient-generated health data that complement our subjective preoperative exams with new objective and longitudinal metrics, and mobile applications are providing valuable insights into outpatient activity levels, psychological stressors and dietary habits.

Through application of these big and small data tools, preoperative risk stratification, patient monitoring, clinical decision support and perioperative medicine initiatives, such as Enhanced Recovery After Surgery (ERAS), can be advanced beyond empirical protocols to create personalized data-driven algorithms that optimize individual patient outcomes. In this chapter, we review how data science and artificial intelligence is currently playing a role in personalized anesthesiology and perioperative medicine, as well as lay out a vision for the future directions of this growing field.

Big Data and Electronic Health Records

Big data and machine learning algorithms for multivariate modeling have been applied in recent years to predict surgical patient risks, diagnose disease and guide patient management using patient demographics, comorbidities, laboratory results, medications and other patient data found in electronic health records. Many of these algorithms, while still at the exploratory research stage, have outperformed the current standards of care or expert clinicians in comparative studies. Targets of machine learning algorithms in the perioperative environment have included development of dynamic clinical metrics, predictions of surgical outcomes and complications (e.g. perioperative bleeding), mortality predictions and more recently, real-time indicators and predictors of patient hemodynamic status, such as hypotension prediction index (Hatib et al. 2018).

Due to the wide range of outcomes and predictor variables included in existing perioperative machine learning models, there is only limited high quality, randomized controlled data to support implementation of these technologies. However, a 2018 systematic review of neurosurgical machine learning algorithms for a range of outcomes found a median accuracy of machine learning predicted outcomes of 94.5% with an absolute improvement in accuracy of 15% over logistic regression. Input features of the 30 machine learning studies in this systematic review included electronic health record data, such as patient demographics (age, sex, symptoms, signs, disease history, family history, medicine usage), radiological images, EEG

Fig. 16.1 Big data in personalized anesthesiology and perioperative medicine

recordings, microelectrode recordings, pathology reports, surgeon volume and hospital volume (Senders et al. 2018) (Fig. 16.1).

Small Data and Consumer Health Devices

While an enormous amount of patient data exists in electronic health records and other big data repositories, personalized healthcare is also dependent on the digital traces that we don't often collect. Data contained in consumer health products, mobile applications and social media accounts are often ignored by our healthcare system, but contain high volumes of objective and calibrated data about our individual patients. These digital fingerprints, known collectively as "small data", are key components to personalized perioperative medicine.

IBM Watson estimates that each person generates over one million gigabytes of health-related data in their lifetime. This patient-generated health data (PGHD) coming from fitness trackers, heart monitors, wearables and mobile applications is invaluable for modeling individual health status. For high-risk surgical patients, PGHD can be used not only for predictive risk modeling, but can also help guide preoperative optimization, i.e. prehabilitation, and calibrate evidence-based guidelines for improved perioperative outcomes, such as ERAS protocols.

However, there are limitations of our current healthcare system for implementation of systems that integrate small data. In a 2018 review of barriers to the clinical use of PGHD, investigators found data structure, data completeness, reliability, measurement context, information overload, interoperability and workflow to be the most commonly cited barriers (Petersen and DeMuro 2015; Zhu et al. 2016; West et al. 2017; Abdolkhani et al. 2019) (Fig. 16.2).

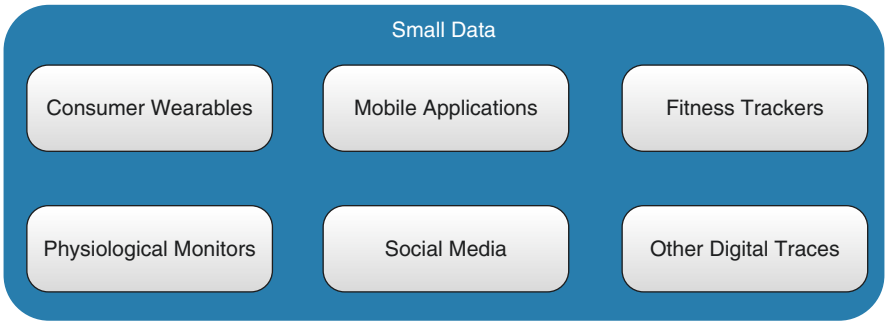

Fig. 16.2 Small data in personalized anesthesia and perioperative medicine

Techniques in AI

Artificial intelligence (AI) is generally taught as containing several subfields, including learning methods (such as machine learning and deep learning), natural language processing, speech and image recognition and expert systems to name a few. In this chapter we will focus on AI learning methods and their application to personalized anesthesiology. Machine learning (ML) was defined by Arthur Samuel in 1959 as the "field of study that gives computers the ability to learn without being explicitly programmed" (Samuel 1959; Connor 2019). Historically, fuzzy set theory and fuzzy logic, in which rule-based algorithms are used with probabilistic categorizations of features, were predecessors to machine learning that required human input to explicitly define rule sets. Instead of explicit rule definitions, machine learning algorithms use input features and data properties to learn how to perform a task through processes known as supervised learning, unsupervised learning or reinforcement learning.

Supervised learning which is found in classical machine learning, is the process of training an algorithm with data features to predict a specified output. Examples of supervised learning algorithms include k-nearest neighbor, naive Bayes, support vector machines, decision trees and neural networks. Conversely, unsupervised learning is used to identify patterns and clusters in data without specifying an output. Some common algorithms for unsupervised learning are self-organizing maps and k-means clustering. Lastly, reinforcement learning algorithms, such as Monte Carlo methods and temporal-difference learning, use a process of trial and error to continually improve on their performance of a task. Supervised learning, unsupervised learning and reinforcement learning are all capable of performing the classification and prediction tasks that are commonly found in healthcare, and the selection of which specific AI technique to use is often determined by the data size and dimensionality, functional complexity, computational bandwidth and operator expertise.

Machine Learning

The most common form of AI used in clinical settings is supervised machine learning. While hundreds of specific machine learning techniques have been developed for optimization of accuracy, performance and fitting, four of the fundamental techniques include linear regression, logistic regression, decision trees and random forests. Linear regression uses a model that predicts a continuous outcome as a weighted sum of the input variables. Conversely, logistic regression is used for classification problems to assign inputs to a discrete set of outcome categories. Decision trees, otherwise known as Classification and Regression Trees (CART), partition input variable data into subsets with homogenous outcome values. Lastly, random forests are ensemble learning methods that fit a plurality of decision trees to subsets of input variable data to achieve improved performance.

Neural Networks and Deep Learning

Artificial neural networks (ANN) are also commonly used in healthcare AI applications. Neural networks mimic the biological interconnectivity of neurons to create a weighted, directed graph of nodes with an input layer, output layer and varying number of hidden layers where computation is performed. In deep learning, neural networks contain several hidden layers, while traditional neural networks may contain up to three (Fig. 16.3).

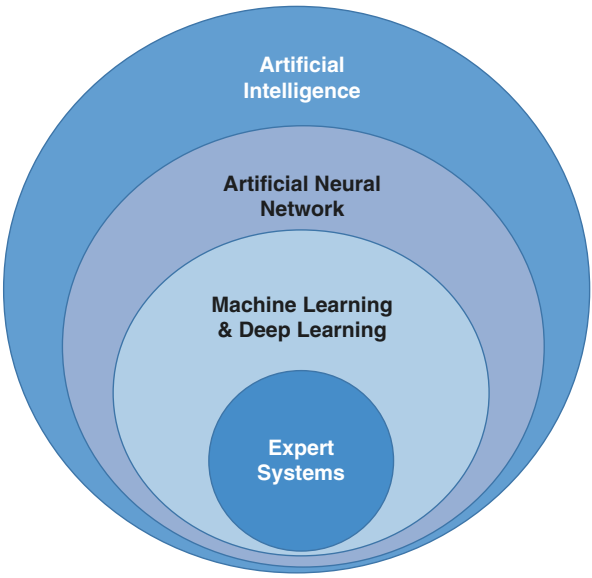

Fig. 16.3 A summary of AI hierarchy; from Rahmatizadeh S, Valizadeh-Haghi S, Dabbagh A. The Role of Artificial Intelligence in Management of Critical COVID-19 Patients. J Cell Mol Anesth. 2020; 5(1): 16–22; with permission (Rahmatizadeh et al. 2020)

Preoperative

Perioperative complications are a major cause of preventable morbidity and mortality after critical illness or surgery but many of the mechanisms continue to be poorly understood. Recent strategies have moved towards characterizing patients' health status preoperatively. There is an increasing possibility to leverage large volumes of unique preoperative data, including patient-generated health data, using artificial intelligence. This requires large-scale, unobtrusive, high quality continuous data collection from the patients' natural environment, and from multiple domains (e.g. heart/motor/brain activity, temperature, circadian/sleep patterns, food intake and physical activity). Put simply, artificial intelligence allows us to use everything about the patient's present state to predict a future state (i.e. perioperative morbidity and mortality). Advancements in health data processing, biosensors, genomics, and proteomics all will help provide a complete picture of a patient which will enable perioperative intelligence. The potential applications are vast, and include prehabilitation and rehabilitation, individualization of perioperative guidelines (ERAS protocols), risk stratification and risk management. These can incorporate not only well established comorbidities relevant to perioperative care, but also unique biomarkers such as circadian/sleep regulation, autonomic function, and genetic risk. All of these interact and are modulated by lifestyle factors.

Artificial intelligence techniques will allow the development of integrative physiological biomarkers that incorporate genetics, circadian biology, physical activity, diet and co-morbidities to predict important postoperative complications. In particular, there is increasing recognition for the link between patients' perioperative outcomes and their prior sleep and circadian health. For example, there is emerging evidence for the potential role of circadian/sleep disturbances in the risk for delirium (Dessap et al. 2015). A fundamental aspect of physiological functions, including sleep, is the adherence to ~24 h cycles, known as circadian rhythms. Circadian/sleep disturbances are more common in the elderly, becoming more pronounced after critical illness (Brainard et al. 2015), and in neurodegenerative diseases such as Alzheimer's disease (AD) (Musiek et al. 2018), groups most vulnerable to delirium. Using wearable technology and actigraphy, personalized machine learning models of sleep-wake states outperform their generalized counterparts in terms of estimating sleep parameters and are indistinguishable from more time-consuming polysomnography labeled sleep-wake states. These personalized machine learning models can be used in actigraphy studies of sleep health, potentially screening for sleep disorders such as insomnia, sleep apnea, narcolepsy or restless leg syndrome known to impact postoperative outcome metrics such as cognition, pain, surgical site infections, and length of recovery or even patient satisfaction.

Preoperative genomics is another area that can leverage artificial intelligence techniques to reveal biological insight into why certain patients experience drastically different postoperative outcomes. Using genetic variability, a way to assess preoperative risk for important responses to perioperative stress is an active area of research. Clinical outcomes include neurocognitive dysfunction, bleeding,

myocardial injury, stroke, infections, acute kidney injury and many others. The ability for artificial intelligence to combine genomic advances with circadian/sleep biology, lifestyle factors and existing comorbidities and their multitude of complex interactions, is an exciting prospect.

Intraoperative

In the intraoperative phase of care, there are numerous applications for artificial intelligence that have the potential to improve perioperative outcomes and personalize anesthetics.

Depth of anesthesia monitoring is one application of artificial intelligence that has already shown promise. The majority of depth of anesthesia studies have focused on the use of the BIS (Medtronic, USA) or electroencephalography (EEG). This has borne out of research efforts to reduce the risk of intraoperative awareness and previous literature suggesting that low BIS and burst-suppression on electroencephalography during anesthesia may be associated with poorer outcomes. For example, excess depth may contribute to suppressed intraoperative mean arterial pressure which has been associated with postoperative mortality. Machine learning approaches are well-suited to analyze complex data streams such as EEG. Studies starting in the 1990s described discriminating awake versus anesthetized patients by using neural networks to evaluate EEG power spectra, and in particular, specific frequency bands as a signal seen in commonly used anesthetic drugs. The use of index parameters of depth of anesthesia (e.g. BIS) increased in popularity, such that neural networks and other machine learning approaches were used to analyze EEG data with the goal of approximating BIS through multiple electroencephalography parameters of increasing complexity.

More recent papers have used artificial intelligence techniques and spectral analysis to more directly analyze EEG signals to estimate the depth of anesthesia. Mirsadeghi et al. studied patients and compared the accuracy of their machine learning method of analyzing direct features from EEG signals (e.g., power in different bands [delta, theta, alpha, beta and gamma], total power, spindle score, entropy, etc.) in identifying awake versus anesthetized patients against the BIS index. Their accuracy in using electroencephalography features was 88.4% while BIS index accuracy was 84.2% (Mirsadeghi et al. 2016). Similarly, Shalbaf et al. used multiple features from EEG to classify awake versus anesthetized patients (as four possible states of awake, light, general, or deep anesthesia) during sevoflurane with 92.91% accuracy compared with the response entropy index which had an accuracy of 77.5% (Shalbaf et al. 2013). This same algorithm demonstrated with generalization to Propofol and volatile anesthesia patients with 93% accuracy versus the BIS index's 87% accuracy. Other clinical variables such as heart rate variability have been investigated to approximate sedation level (Nagaraj et al. 2017). These studies highlight the power of artificial intelligence techniques in creating

models that can efficiently consider linear and non-linear data simultaneously to generate maximal prediction value.

Related to depth of anesthesia monitoring, there has been increasing interest in the control of automated anesthesia delivery. Control systems using machine learning have also been used to automate the delivery of neuromuscular blockade, where these systems have also incorporated forecasting of drug pharmacokinetics to further improve the control of infusions of paralytics. Other applications include the use of artificial intelligence to achieve control of mechanical ventilation or to automate weaning from mechanical ventilation.

For perioperative care risk prediction, various techniques in machine learning, neural networks, and fuzzy logic have been applied. For example, neural networks used to predict the hypnotic effect (as measured by BIS) of an induction bolus dose of propofol were found to exceed the average estimate of practicing anesthesiologists (Liu et al. 2019). Neural networks have also been used to predict the rate of recovery from neuromuscular blockade and hypotensive episodes post-induction or during spinal anesthesia, while other machine learning approaches have been tested to automatically classify pre-operative patient acuity (i.e., ASA status), define difficult laryngoscopy findings, identify respiratory depression during conscious sedation, and to assist in decision-making for the optimal method of anesthesia in pediatric surgery (Lin et al. 2002). Waveform data from arterial lines has been used to develop models that could predict hypotension before their occurrence on an arterial line waveform (Hatib et al. 2018). Others have used machine learning models to predict morbidity/mortality, sepsis, weaning from ventilation, or readmission.

Imaging guidance has also benefited from using convolutional neural network to identify key vessels e.g. femoral artery/vein during a femoral nerve block, vertebral level, lamina or epidural space during real-time (Hetherington et al. 2017). Pain management may improve with the use of machine learning to measure nociception levels based on photoplethysmograms and skin conductance waveforms or EEG (Hamunen et al. 2012; Pesteie et al. 2018).

Finally, even operating room logistics has benefitted from improved prediction of operation duration, bed usage, recovery throughput and length of recovery using a combination of information on staffing characteristics both anesthesia and surgical, and patient medical history (Gram et al. 2017). In these myriad of potential applications, anesthesiologists should continue to partner with data scientists and engineers to provide their valuable clinical insight into the development of artificial intelligence to ensure its clinical applicability, training data validity, generalizability, and that interpretations of that data are clinically meaningful.

Postoperative

In the postoperative setting, artificial intelligence and telehealth are playing increasingly important roles in disposition and reducing length of stay. Remote monitoring technologies and early warning systems, such as AlertWatch® (Tremper et al. 2018),

are transforming postoperative care by reducing ICU admissions and alerting responding clinicians prior to patient decompensation. Postoperative monitors that combine artificial intelligence with plethysmographic and electrocardiographic signals have been developed for noninvasive respiratory and hemodynamic monitoring. Additionally, consumer health wearable devices are providing new sources of patient generated health data for post-discharge monitoring and rehabilitation programs.

Future Directions of AI in Personalized Anesthesiology

As degrees of freedom in a dataset increase, machine learning and deep learning algorithms require larger training datasets to develop accurate models. This means that as our patient datasets become larger and more complex, we'll need more patients to predict outcomes and to leverage all of the available big data and small data resources. Personalized anesthesiology that leverages both electronic health record data and patient-generated health data is on the horizon, but will require collaborative initiatives between academic medical centers to minimize biases and ensure generalizable models. Perioperative data consortiums, such as Multicenter Perioperative Outcomes Group (MPOG), will be critical to the integration of artificial intelligence into the perioperative ecosystem (Kheterpal 2011; Simpao et al. 2015).

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Chapter 17
The Role of Education in Personalized Anesthesiology, Pain and Perioperative Medicine

Samira Rajaei and Ali Dabbagh

Introduction

Nowadays, the personalized medicine approach has started its migration from "bench to bedside", finding its path in our daily clinical practice. However, is the status of education coping with this "Fast and Furious" trend? Is the trend of medical education coping with this paradigm shift? The current evidence shows that we have to consider some degrees of reform in undergraduate, postgraduate and Continuing Medical Education (CME) to cope with these changes (Eden et al. 2016).

The Accreditation Council for Graduate Medical Education (ACGME) has stressed on the following competencies as the main 6 core competencies in medical education (Miller 1990):

- Practice-Based Learning and Improvement
- Patient Care and Procedural Skills
- Systems-Based Practice
- Medical Knowledge
- Interpersonal and Communication Skills
- Professionalism

Here, the integrated and bilateral interaction between "medical education"and "personalized anesthesia and perioperative medicine" is discussed in order to make

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the audience much more familiar with this issue and also to highlight the potential solutions for coping with paradigm shift (Dabbagh and Elyassi 2016; Sezari and Dabbagh 2019; Rajaei and Dabbagh 2020).

To cope with the inevitable changes in near future and reach a more tangible approach, this chapter stresses on the necessity and the methods for curricular revision with especial focus on medical education in anesthesiology and perioperative medicine. The domains mentioned in this chapter are the main fields for curricular reform and program change in medical education; though some aspects may be missing and the audience may refer to medical education texts for detailed reading. Each individual curriculum should modify its content, approach, potential and actual capacities and, attitudes and practice of department members throughout the following topics, if it wants to sustain in the current competitive outcome-based era of medical education (Spencer et al. 2008; Irby et al. 2010; Eisenstein et al. 2014b; Mirzazadeh et al. 2014; Kulasegaram et al. 2018; Mortaz Hejri et al. 2018):

- Concepts and approaches
- Admission of trainee
- Appropriate and measurable outcomes
- Superior, comparable and effective competencies
- Educational content and strategies
- Teaching and learning methods
- Trainee assessment
- Faculty development
- Program evaluation
- Curriculum management
- Managerial andGovernance structure
- Process of leading change

Concept and Approach

In the current epoch of multilateral paradigms, policy scientists believe that "science-based problem-solving"mandates "interdisciplinary research". Many science philosophists believe that in a very strong epistemological basis for the role of interdisciplinary research in science-based problem-solving. So, both the scientific community and the policy makers have shifted towards interdisciplinary approach to resolve the world's largest challenges (Schmidt 2011; O'Rourke et al. 2016; Boon and Van Baalen 2019).

The shift from distinct divided sole disciplinary approach to interdisciplinary team working has started a few decades ago, reaching an up-roaring in the mid-1980s; nowadays, leading to a number of novel approaches including the following.

- Problem-Oriented Interdisciplinarity
- Interdisciplinary Evidence-Based Practice
- Interdisciplinary Scientific Collaboration

- Assembly of Interdisciplinary teams
- Scientific Team Functioning
- Advanced Translational Science

The most common feature in all of these novel approaches is boosting synergy leading to improved outcomes, impact and performance (Newhouse and Spring 2010; Schmidt 2011; Lungeanu et al. 2014; Ledford 2015; Van Noorden 2015; Guerrero et al. 2017).

The same process has been followed in medical education, not only to increase the quality and efficiency of medical education and training process, but also to improve the final outcome of medical education; i.e. patient care (Rajaei and Dabbagh 2016; Hitziger et al. 2018). However, the process of interdisciplinary approach is much more than just putting a number of different colleagues alongside; as seen in Fig. 17.1. Instead, a real merge in both conceptual and contextual frameworks, ideals, goals and missions is the cornerstone of interdisciplinary teamwork (Stokols et al. 2008; Newhouse and Spring 2010; Lungeanu et al. 2014) (Fig. 17.2). "Personalized anesthesiology and perioperative medicine" not only depends on interdisciplinary approach but also augments a practical model of this concept. In fact, advanced models of discipline merging (like interdisciplinary and transdisciplinary models) could both improve the effectiveness of current systems and also, lead to innovative emerging networks (Guerrero et al. 2017; Hitziger et al. 2018).

A number of terms and concepts have been described including interdisciplinary and transdisciplinary approaches which are applicable in healthcare, to research, education and service provision (Figs. 17.1, 17.2, 17.3). In personalized anesthesia and perioperative medicine, many fields could be conducted using team working and merged discipline models; including novel anesthetic agents, pain clinics and

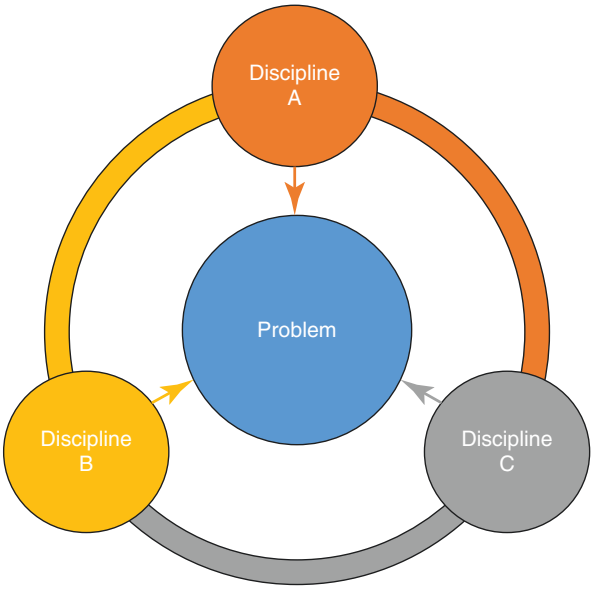

Fig. 17.1 Multi-disciplinary approach. From Rajaei et al.; under the terms of Creative Commons Attribution 4.0 International License; (Rajaei and Dabbagh 2016)

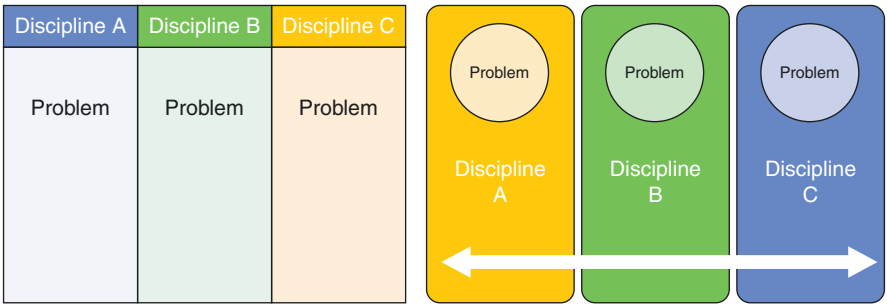

Fig. 17.2 Interdisciplinary approach; (**a**) sequential interdisciplinary approach; (**b**) horizontal interdisciplinary approach. From Rajaei et al.; under the terms of Creative Commons Attribution 4.0 International License; (Rajaei and Dabbagh 2016)

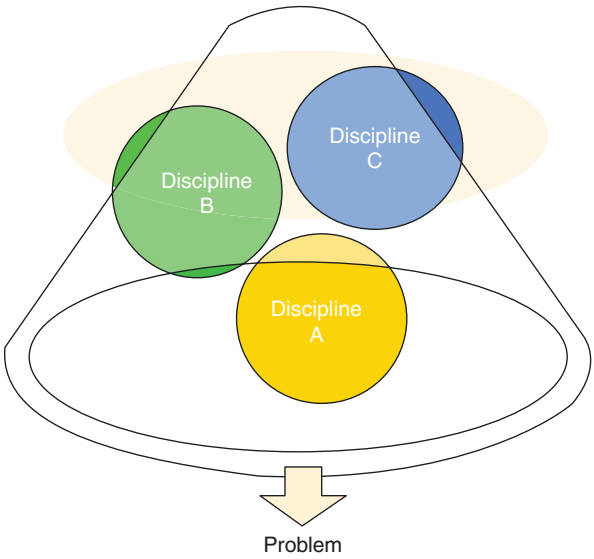

Fig. 17.3 Transdisciplinary approach; Groups A, B and C have a holistic approach to the problem. From Rajaei et al.; under the terms of Creative Commons Attribution 4.0 International License; (Rajaei and Dabbagh 2016)

pain management, pediatric anesthesia, palliative era, cardiac anesthesia, neurologic protection, Enhanced Recovery after Surgery (ERAS) concept and a number of other distinct fields (Binder et al. 2015; Rajaei and Dabbagh 2016). Improving patient safety and risk reduction in both current anesthetics and emerging novel agents are amongst excellent examples of the role that transdisciplinary approach could play in personalized anesthesia (Klein 2008; Binder et al. 2015).

The approach of using "integrated case studies with hands-on laboratory experience" is a practical example of integration; which could range from multidisciplinary to interdisciplinary approaches. In fact, transdisciplinary approaches are currently among the main demands of medical schools; both for undergraduate and

postgraduate medical education (Dahle et al. 2002a; O'Connor Grochowski et al. 2007; Spencer et al. 2008).

Admission of Trainee

The trainee should be informed regarding the "personalized anesthesia and perioperative medicine" from the time of undergraduate learning as elective courses. In complementary steps, the junior residents of anesthesiology and even related specialties could become familiar with this approach. This needs a redesign in many of the undergraduate and postgraduate curricula; including nurse anesthetists. All fellowship curricula in anesthesiology could address the personalized anesthesia and perioperative medicine approach into their programs. On the other hand, the applicants in a residency program should be guided to increase their motivation in learning the topic and also, to perceive the value of these fields for the ultimate goal of improving quality of care (McGrath and Ghersi 2016; Sezari and Dabbagh 2019).

Appropriate and Measurable Outcomes

One of the essential requirements in medical education is to have defined outcomes; no matter it is undergraduate, graduate or continuing medical education (Rosenberg 2018). Outcome measure, known as the Outcome Project, is an essential part of graduate medical education evaluation activities of ACGME (the Accreditation Council for Graduate Medical Education) (Swing 2007; Haan et al. 2008; Rajaei and Dabbagh 2016; Chatterjee and Corral 2017).

One of the most common approaches in designing outcomes is based on the SMART mnemonic (Chatterjee and Corral 2017):

- S: Specific
- M: Measurable
- A: Attainable
- R: Relevant
- T: Time-bound

As stated above, the personalized anesthesia and perioperative medicine approach should focus on definite outcomes, which are both clinical and basic; i.e. improvements in the clinical outcome of the patients with a specific focus on the products of applying basic science in the clinical field. In order to write the outcomes, it is useful to follow practical guidelines in this field; using a number of "outcome writing approaches"that could be found in more comprehensive texts; however, the following tips could be used as practical ones.

First, outcomes should cover all educational learning objectives; for example all levels of the Bloom's Taxonomy (Wachtel and Dexter 2010; Yanofsky and Nyquist 2010; Krau 2011; Konia and Yao 2013; Gill et al. 2019), including:

- the cognitive domain (knowledge-based)
- the psychomotor domain; action-based domain
- the affective domain (emotion-based)

Second, the outcomes should include practical verbs that consider all aspects of the outcome (Spencer et al. 2008; Yeo 2019); in other words, the following domains should be defined and practical verbs be used in each domain in order to write appropriate outcomes of the personalized anesthesia and perioperative course, a full list of the verbs is available in more detailed references and the interested reader could refer to them (Harden 2002; DeRienzo et al. 2012; Armson et al. 2015; Chatterjee and Corral 2017; Yeo 2019):

1. knowledge
2. comprehension
3. application
4. analysis
5. synthesis
6. evaluation
7. receiving
8. responding
9. valuing
10. organizing
11. characterization by a value

Back to Basic Sciences

> Everyone who stays away from his/her origin
> Searches for the time of original connection
> (Rumi; Masnavi, Book 1, Thirteenth-century)

In the era of personalized medicine, there is an increasing need to move back to basic sciences with a main role in personalized anesthesia and perioperative medicine. Integrating basic sciences in clinical field is an innovative and well known approach especially after the Edinburgh Declaration in 1988. Though many benefits would occur after performing cooperation over departmental borders; there may be some challenges that should be overcome. Besides, both cognitive activity and curricular structure should be considered when there is a plan for basic-clinical integration. The practical approaches for implementing this strategy may include the following items though many other creative methods could be used (Dahle et al. 2002b; Eisenstein et al. 2014a; Bandiera et al. 2018; Drozd et al. 2018; Shendure et al. 2019; Pagliaro 2020):

- Teaching basic anesthesia sciences to the trainee as core/elective courses
- Common educational rounds, Case presentation discussing basic and clinical aspects of the selected patients, point by point, in view of both basic and clinical approaches and problem based learning methods on this topic
- organ based teaching; integrated basic and clinical
- postgraduate education; including but not limited to fellowship courses in basic sciences or PhD degrees for anesthesiologists
- Planning and performing integrated research; including integrated research teams; defining integrated field of interest; cooperative research with basic scientists; etc.
- listing the main clinical problems and finding team responses using the above approaches

Though many different approaches could be used, the following are just some examples of using basic sciences in personalized anesthesiology and perioperative medicine:

1. cellular and molecular biology
2. medical physiology
3. clinical anatomy and clinical embryology
4. clinical immunology
5. clinical pharmacology
6. medical microbiology
7. hematology and blood banking
8. genetics
9. epigenetics
10. transcriptomics
11. proteomics
12. metabolomics
13. information technology
14. interactomics
15. medical physics
16. clinical nutrition and dietetics
17. medical statistics

Curriculum Development

The development of a curriculum is a cornerstone in medical education. This task is the responsibility of those involved in the curriculum; i.e. the authorities of the program and needs a scholar and programmed basis. The description of the six step approach is far beyond the scope of this chapter; however, David Kern in his famous book known as “Kern’s six steps of curriculum development“has discussed each of the six steps of curriculum development in a separate chapter, including (Schneiderhan et al. 2019):

1. identifying the problem
2. assessment of the needs
3. declaring the goals and objectives
4. determining the strategies for educational
5. implementing the curriculum
6. evaluation of the curriculum

Superior, Comparable and Effective Competencies

One of the challenging topics in medical education are the competencies and meta-competencies. These basic theoretical aspects of education should be changed to clinical implementations with defined goals, or explicit outcomes. As stated in the beginning of the chapter, ACGME has focused on the main 6 core competencies in medical education (Miller 1990; Holmboe et al. 2016). However, in order to achieve them, an action plan is needed. Harden et al. in 1999 proposed the famous three-circle model of outcome based education (Harden et al. 1999):

1. the inner circle is "*doing the right thing*": *i.e.* what acts the physician should be able to do
2. the middle circle is "*doing the thing right*": *i.e.* what methods is used for doing that and it means the method used by the physician to reach the inner circle
3. the outer circle is "*the right person doing it*": *i.e.* professional development of the individual which indicated the personal factors affecting the person in doing his duties

Eight years later, Harden (Harden 2007a, b) cited the most important prerequisites for achieving outcome based education (OBE) as the two following:

1. learning *outcomes* should be stated explicitly
2. a number of outcomes should be determined and targeted as the "*basis for curriculum*"

However, in the majority of curricula, the second prerequisite is ignored. These studies and concerns, stress the role of curricular design and curricular reform in OBE and also, the impact of education in providing care.

Paving the same road, "education specialists"have been dealing with Competency based education for more than 6 decades; however, in "medical education" it is just a decade or a little more that Competency-Based Medical Education (CBME) has become a prominent point of focus; especially because CBME targets the objective gains of education (Whitcomb 2016; Frank et al. 2017; Powell and Carraccio 2018). CBME utters that medical education should be tailored for each trainee; in other words, medical education should be personalized in such a way that the trainee would be finally capable of performing the task and far beyond that, be accountable about his/her task (Harden 2007b; Orgill and Simpson 2014; Weller et al. 2020).

Now, more than 100 years has passed since the Flexner's transformative report in 1910; and in the current era of cost-effectiveness and competitiveness of medical education, OBE and CBME are in the center of focus more than any other time (Irby 2011).

The practical approach of CBME is defined as a competency fulfilling approach; not a time limited schedule. In fact, in CBME, each trainee would be considered as an exclusive and special project of education; with defined educational goals (Mirzazadeh et al. 2014; Shah et al. 2016). The time frame of the education is flexible and would be continued until the minimum goals are achieved; the education goals are defined as the minimum competency levels for the patient inside the society in such a way the outcome of the patients is targeted (Frank et al. 2010b; Snell and Frank 2010; Brightwell and Grant 2013; Hoff et al. 2018; Schumacher et al. 2020).

However, for implementing CBME, the knowledge, attitudes and practice (i.e. the culture and the atmosphere) of the specific curriculum should be changed (Ferguson et al. 2017).

One of the most common models for implementing CBME is to use Entrustable procedural activities (EPA) and applying milestones as the tools which should be defined according to the target curriculum. Olle Ten Cate's described the concept of Entrustable procedural activities (EPA) first in 2005 to have objective and tangible assessment tools for undergraduate and postgraduate medical education. These are developed in many fields of medical education including anesthesiology to ensure CBME in clinical training; besides, each of the competencies (including the 6 main core competencies) and each of the EPA's in the curriculum could be divided to a number of measurable "quantum's" known as milestones (Frank et al. 2010a; Iobst and Caverzagie 2013; Ten Cate 2013, 2017; Teherani and Chen 2014; Jonker et al. 2015; Wisman-Zwarter et al. 2016; Hoff et al. 2018; Sharma et al. 2019).

If an anesthesiology related curriculum (residency or fellowship) is supposed to be "enriched" with personalized anesthesia and perioperative medicine, a practical revision in that curriculum using CBME elements would be applicable in terms of the medical education outcomes (Desy et al. 2017; Powell and Carraccio 2018). The following steps could be considered as the main steps in this "Personalized Anesthesiology and Perioperative Medicine" reform (Iobst and Caverzagie 2013; Orgill and Simpson 2014; Stodel et al. 2015; Carraccio et al. 2017; Weggemans et al. 2017; Chemtob et al. 2018):

1. The process of CBME reform and designing EPA though a departmental project, needs a defined career roadmap with institutional support (Ebert and Fox 2014)
2. A taskforce should be established in the "Personalized Anesthesiology and Perioperative Medicine" committee of the Department, preferably including faculty members and trainee representatives added by medical education specialists; in this regard, faculty development programs should have been already designed and implemented in such a way to endorse CBME basics and skills (Fraser et al. 2016)

3. It is suggested that in later steps, a number of the other Anesthesiology Departments throughout the country be involved to increase the external validity of the process; also, some external bodies like ACGME in United States or similar organizations in other countries
4. Adopting the international approaches, a local modification is needed to cope with departmental goals
5. The most common and the most important topics of the target curriculum should be selected; different methods including using a Delphi questionnaire could be considered to prepare the primary list of EPA's
6. A multi-step characterization table should be defined for each EPA, based on the 6 core competency defined by ACGME; the main topics in this table could be "Specification", "Relevant Competency Domain(s)", "Required Knowledge Content", "Minimum Required Skills", "Attitudes and Experience", "Sources of Information to Assess Progress" and "Expected Entrustment or Supervision Level" (Jonker et al. 2015; Wisman-Zwarter et al. 2016; Cate 2018)
7. For each single EPA, a draft should be prepared by each of the taskforce members, alone or in combination with other colleagues
8. Each of the EPA's should be defined as measurable milestones
9. The drafts should be discussed, critically appraised and thrived; regarding both content and the format of each EPA with its milestones; this step could be done in smaller and then larger groups with formative discussions
10. In the next step, all the faculty members of the department as stakeholders of the EPA's are preferred to be involved in all EPA drafts
11. The drafts should be edited, revised and finalized as pilot draft of EPA's for a semester or two during which, the EPA's have been assessed and the milestones have been checked; then, the above steps should be repeated to improve them
12. This process should be followed to reach a full coverage curriculum period

Each of the competencies (including the 6 main core competencies) and each of the EPA's in the curriculum could be divided to a number of measurable "quantum's" known as milestones which incorporate formative assessment and periodical direct and indirect feedbacks to the trainee (Teherani and Chen 2014; Desy et al. 2017).

Though the CBME-based curricular reform approach is still novel and there are some controversies, it could lead to tangible results if applied timely and with a delicate program; leading to superiority of the graduates though some authors suggest more research in order to reach conclusive result (Ten Cate 2017; Bisgaard et al. 2018; Weller et al. 2020).

Teaching and Learning Methods

There is an emerging need to use a list of different training methods especially for personalized anesthesia and perioperative medicine; since this shift in medicine needs a revision in medical education in such a way that the trainee could

compensate for their potential defects in knowledge and practice that has been created in the recent years. The needed list for novel approaches in medical education includes theoretical didactic courses to different e-learning approaches for education, and to "hybrid education and multidisciplinary teams"; all should be tailored for the trainee(s); there is no "one-size-fits-all"answer for the method of training in personalized anesthesia and perioperative medicine since one size does not fit all trainee (Welke et al. 2009; Alyass et al. 2015; Mason-Suares et al. 2016; Yamamoto et al. 2017; Connor 2019; Fadaizadeh et al. 2019; Rahmatizadeh et al. 2020). There is undoubtedly a major educational role for the "trainee assessment and evaluation tools"as teaching and learning methods. These would be discussed in the next sections.

Trainee Assessment and Evaluation

Like many other courses in graduate medical education, the process of trainee assessment and evaluation is a main method for teaching and learning; both throughout (formative assessment) and at the end of the course (summative assessment). For this purpose, assessment and evaluation could be divided arbitrarily to the following steps (Fluit et al. 2012; Myers et al. 2012; Geffen 2014; Ghasemzadeh et al. 2015; Schiekirka et al. 2015; Dabbagh et al. 2019, 2020):

- Collecting data from the trainee
- "Curriculum outcomes", "psychometric characteristics of the evaluation tools; including validity and reliability of measurement" and "confounders of evaluation" are among the most important determinants that should be considered all over the evaluation process
- Checking the collected data and the measurement tools
- Analyzing the results
- Assessment of the results (individually, inside the group and the total trainee team)
- Making decisions based on processed information
- Giving feedback to the trainee
- Clarity of the assessment/evaluation process
- Temporary, stepwise and global crediting

The above items should be an integral part of assessment in each of the 4 levels of the famous Miller's Pyramid: the layers are "Knows," "Knows how," "Shows how," and "Does" leading to a thorough assessment of knowledge, attitudes, skills, and behaviors and the final patient-related outcomes (Fig. 17.4) (Miller 1990; Cruess et al. 2016; Williams et al. 2016).

Methods of evaluation could be either objective or subjective; they could be qualitative or quantitative and they may be written (MCQ's, True/False, Essay, Modified Essay Question, modified Constructed Response Question), oral or web-based; each of them has its merits and drawbacks. Among a long list of methods for trainee assessment and evaluation, the following could be mentioned as methods of

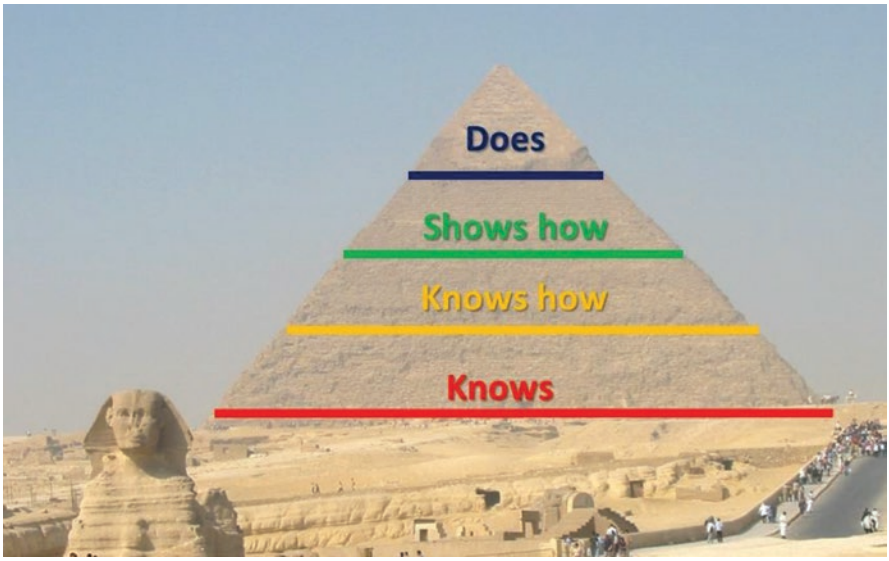

Fig. 17.4 Miller's Pyramid and its layers

assessing a wider range of competency aspects. However, it is a direct result of art and experience of the evaluator and/or assessor to combine a list of options from following methods or any other methods to create a valid, reliable, acceptable, user-friendly and cost-effective assessment plan that not only yields sound assessment results, but also, benefits the outcome of education for trainee, gives constructive feedback to the faculty and improves the whole curriculum. For personalized anesthesia and perioperative medicine, add to the above, a novel personalized viewpoint towards anesthesiology that creates a new atmosphere of assessment/evaluation (Buckwalter et al. 1981; Downing 2002; Morrison 2003; Davis et al. 2006; Epstein 2007; Reid et al. 2007; Tarrant and Ware 2008; Dubinsky et al. 2010; Cook et al. 2011; Boulet and Murray 2012; DeMaria et al. 2013; Mundell et al. 2013; Boet et al. 2014; Kurtz et al. 2019; Miller et al. 2019; Dabbagh et al. 2020):

- Oral assessments
- Written assessment: MCQ's, True/False questions, Essay, Short Answer Questions (SAQ), Modified Essay Question (MEQ), Constructed Response Question (CRQ's)
- mini-CEX (Mini Clinical Evaluation Exerciser)
- Directly Observed Procedural Skills (DOPS)
- Clinical work sampling (CWS)
- Regular maintenance of periodical standard written and MCQ's exams with feedback and assessments analysis
- Students' Logbook and portfolio (both for the clinical field and the so-called lab fields)
- OSCE and Simulated exams

- Technology-enhanced Simulation
- 360-degree Physician Performance Assessment
- Targeted problem based learning (PBL) classes
- Role playing for residents (Peer role playing)
- Role playing using simulated patients and case scenarios
- Peer assessment
- Patient assessment
- Self-assessment

Mentorship for Trainee

Mentoring is considered a relatively avant-garde method in graduate medical education though it has been used for longer time in higher education (Stenfors-Hayes et al. 2011; Banu et al. 2016).

The goal of mentoring in graduate medical education is similar to undergraduate medical education; including improving knowledge, attitude, practice, behavior, professionalism, research opportunities and the final impact of the curriculum. In addition, improving the performance gap is one of the main goals in graduate medical education mentoring (Dalgaty et al. 2017). Besides, being interested in a specialty or sub-specialty may be due to the scientific and professional effects of the mentor (Stenfors-Hayes et al. 2011; Farag et al. 2012; Wenzel and Gravenstein 2016).

However, could every faculty member or senior resident be a good mentor? The answer is possibly "No". Being mentor is a capacity needing thriving and development. Ramani, et al. have described 12 important and practical tips for "developing effective mentors", based on the latter study and the other ones, a brief list is presented that encompasses the essential characteristics of the mentoring program for graduate medical education (Ramani et al. 2006; Farag et al. 2012; Straus et al. 2013; Alisic et al. 2016; Faucett et al. 2017; Dabbagh et al. 2019):

1. The role of mentors should be defined clearly
2. Continuous evaluations of their function and giving feedbacks to the mentors are integral parts of the mentoring program
3. Mentors should be supported, both scientifically and psychologically
4. Mentors should be mentored! Each mentor needs a mentor
5. Mentors should be raised, valued and rewarded
6. Mentors should both support and challenge the mentees
7. Gender and culture are important issues in mentoring; same gender and similar culture should be considered and available
8. Mentors should behave in a completely professional manner
9. The timetable for mentor and mentee should be programmed and delicate
10. Peer mentoring or near-peer mentoring should part of the mentoring pyramid

In personalized anesthesiology and perioperative medicine, the mentors could play a crucial role in improving the performance and outcome of the trainees (Flexman and Gelb 2011; Farag et al. 2012; Gonzalez and Donnelly 2016).

Faculty Development

One of the highly effective methods for improving the faculty and the whole department is applying a faculty development program (FDP); especially when novel ideas are going to be incorporated in the traditional curriculum. There are a number of definitions for Faculty Development; all of them however, consider a dual role for FDP's (Drucker 1999; Hamilton and Brown 2003; Steinert et al. 2006; McLean et al. 2008; Zerzan et al. 2009; Ries et al. 2012; Fraser et al. 2016; Souter 2016):

- improvement in the academic, scientific, teaching/education, research, health care provision, professionalism and leadership competencies of the individual faculty members
- fulfilling the goals and missions of the institution

For example, FDP's are among the most important prerequisites for CBME which has been discussed in previous sections in detail. Or from another point of view, in those departments who wish to run their personalized anesthesia and perioperative medicine section, one of the most effective steps would be using FDP.

A wide variety of FDP's have been introduced including models of mentorship for junior attending. If an appropriate approach is chosen, many benefits (including the following) would ensue:

- Improved knowledge and skills of the faculty
- Positive change in the attitudes of the faculty
- Improvement in faculty teaching and learning pattern
- Increased outcome of education regarding trainee perspectives
- Motivated scholar activities of the faculty with definite goals and specific novel fields of interest, leading to improved scholar activities

How to design FDP's? There is a 6 step module for curriculum planning in medical education that is very useful to be followed for developing FDP's and the interested reader is suggested to refer to these materials. However, FDP's should be based on a systematic sustained platform; including appropriate design, delicate implementation tailored for the audience group, systematic evaluation and assessment of the outcomes and continuous regular feedbacks. (McLean et al. 2008; Souter 2016).

However, the FDP's should be chosen appropriately and also, the challenges of the program should be managed, both by the faculty members and the affiliated department and/or institution. FDP if performed appropriately leads to a boosted movement in the personalized anesthesia and perioperative medicine approach of a department including both educational outcomes and the quality of

patient care. The contents and the time schedule of the FDP's depend on the goals and missions of the department; including the goals for improving personalized anesthesia and perioperative medicine; so, in this approach, faculty development not only includes scholar, research and academic activities but also should incorporate "change leadership capacities" for the faculty members in such a way they would be able to conduct the process of transition to "personalized anesthesia and perioperative medicine" (Steinert et al. 2006; Jackevicius et al. 2014; Lancaster et al. 2014; McEvoy et al. 2016; Mitchell and Jones 2016; Guillet et al. 2017).

Curriculum Management, Curriculum Monitoring and Curriculum Evaluation

There should be a genius design for dynamic control of the curriculum, whether in residency and/or fellowship programs, undergraduate students or CME courses. This dynamic control has 3 processes which have parts in common:

- Curriculum management
- Curriculum monitoring
- Curriculum evaluation

Curriculum management is the most suitable tool in order to ensure correct implementation of each curriculum (Changiz et al. 2019). Based on the definition provided by Stansbury and Huenecke, curriculum management included 4 ingredients (Harden 2001; de Bruin et al. 2017; Changiz et al. 2019):

1. The goals of the curriculum should be determined and set up precisely
2. A specific and definitive action plan should be defined in such a way that ensures achieving the latter goals
3. For implementing the above action, an orderly designed and documented management process should be firmed
4. All the above 3 steps; i.e. "determining goals", "the action plan for achieving goals" and "the managerial processes" should be audited, evaluated and revised in specific time-based and goal-based intervals

Curriculum monitoring involves a sustained process of data collection, assessment, evaluation and feedback, considering previous and current situation and targeting the determined goals; with especial focus on outcome. In this process, the level of meeting standards in the curriculum and the amount of target achievement are a main part. In other words, curriculum monitoring is the ongoing and continuous quality check of the curriculum, in order to ensure conquering the goals. If the curriculum does not work properly, this process may even lead to curriculum revision (partial or total revision); in the minority of the cases, even may lead to stopping the curriculum (Harden 2001; de Bruin et al. 2017; Lammerding-Koeppel et al. 2017; Changiz et al. 2019).

Curriculum evaluation is a process of judgment about the worth of the curriculum; its prominent feature is that curriculum evaluation focuses on both the defined values and goals and the perceived outcomes. Though there are many aspects of monitoring and evaluation in common, the former considers the past, present and future status of the program while the evaluation process commonly has a retrospective approach The goal of evaluation, its design and the practical methods, the measured values, the ethics of evaluation, interpreting the results and disseminating them are among the main concerns in curriculum evaluation. However, and this is the prominent feature. (Goldie 2006; Changiz et al. 2019).

In the current epoch of artificial intelligence (IT), using e-Management, e-Monitoring, e-Evaluation and all IT-based methods have made these processes much more rapid and robust with higher degrees of effectiveness for assessment and decision making; the use of AI in Personalized Anesthesia and Perioperative Medicine has been discussed in another chapter of this book (Watson et al. 2007; Guze 2015; Wartman and Combs 2018; Duong et al. 2019; Masters 2019; Hashimoto et al. 2020).

Curriculum management, curriculum monitoring and curriculum evaluation lead to invaluable information that could be provided to the curriculum authorities for the next steps. As mentioned in previous paragraphs, the most important prerequisites for achieving OBE are the two following items, based on studies by Harden, while the second item is often ignored (Harden 2007a, b):

1. learning outcomes should be stated explicitly
2. a number of outcomes should be determined and targeted as the "basis for curriculum"

The ultimate goal of OBE and the outcome of education in providing care could not be fulfilled unless the information from curriculum management/monitoring/evaluation would be used in curricular design and curricular reform.

Managerial and Governance Structure and the Process of Leading Change

Besides all the above approaches, there should be a leadership support. This needs a designed and structured level of support at the department head, extending to the academic and managerial authoritative levels of the medical school and the academic medical centers in which the personalized anesthesia and perioperative medicine program is running. However, this should not be just a written hierarchy; instead practical contribution from all stakeholders are needed.

This governing structure should be dynamic with prospective approaches towards improved outcome based education. Being familiar with the concepts, the authoritative body should be both proactive and inspiring. However, a great degree of self-regulation should be given to the department and the involved faculty.

A designed plan of monitoring, assessment and evaluation should be prepared with defined time intervals for all auditing tasks. However, all these approaches are among the armamentarium to reach the ultimate goal: "reaching a developed personalized anesthesia and perioperative medicine curriculum that leads to improved outcomes, enhanced trainee competencies and improved patient care".

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