The High-Risk Pediatric Surgical Patient

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Key Points

- Perioperative morbidity is the result of an interplay between patient characteristics, comorbidities, and intrinsic surgical risk.
- Anesthesia-related death is rare, and patients with significant life-threatening medical problems are at the highest risk.
- Due to higher interrater variability, many risk-assessment scores have been developed in order to estimate the perioperative risk in children.
- The highest risk patients include: the neonate, the child with congenital heart disease, the child with pulmonary hypertension, and the child with respiratory disease.
- Neonates and infants have limited physiological reserve, and are at greater risk of complications with general anesthesia, with premature neonates being at the highest risk of physiologic instability.
- Children with major and severe congenital heart disease undergoing noncardiac surgery have an increased risk of mortality as do children with pulmonary hypertension.
- Preoperative multidisciplinary care of high-risk pediatric patients, identification of risk factors, and perioperative optimization are essential elements in decreasing post-operative mortality and in improving post-operative outcomes.

11.1 Introduction

The incidence of perioperative mortality in the pediatric surgical population is low, estimated at 0.1–1.2 per 100,000 anesthetics delivered [1–7]. Perioperative mortality is the result of an interplay between patients' comorbidities and intrinsic surgical risk (ISR) [8]. Intraoperatively, the cardiopulmonary, endocrine and hemodynamic physiological responses to surgical stimulation and tissue disruption are, among other factors, the major determinants of surgical risk. In addition to mortality, a basic measure for quality and safety in anesthesia, pediatric patients are at risk of morbidity including but not limited to neurologic decline, prolonged mechanical ventilation, and unanticipated escalation of care. Thereafter, a better understanding of the incidence and risk factors for perioperative mortality and morbidity guides the anesthesiologist in identifying the high-risk patient preoperatively. Identifying high-risk patients will allow for adequate case planning, expert staffing, and appropriate resource allocation. It will also provide the family with objective evidence-based counseling and a well-informed consent for anesthesia [9].

This chapter will review the anesthesia-related morbidity and mortality, the risk factors, and special considerations in high-risk pediatric patient population.

11.2 Anesthesia-Related Morbidity and Mortality

With the advancements in medical therapies and advent use of sophisticated extra-corporeal cardiorespiratory support systems, patients with highly complex medical problems are increasingly presenting for surgery and other procedures, such as medical imaging. We will discuss in the sections below the risk of perioperative morbidity and mortality.

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11.2.1 Perioperative Morbidity

The determinants of perioperative risk in children are complex and multifactorial. Perioperative morbidity is believed to be the result of an interplay between patient characteristics, comorbidities, and ISR [8, 10]. The ISR is the 30-day mortality risk for specific surgical procedures independent of comorbidities. It takes into consideration the perioperative physiologic responses of the cardiovascular, pulmonary, endocrine, coagulation, and immune systems resulting from surgical tissue injury. In addition, the complexity and duration of surgery play a direct impact on the intraoperative hemodynamic changes caused by blood loss, core temperature variations, fluid shifts, and mechanical alteration of organs [8, 11].

The Anesthesia Practice in Children Observational Trial (APRICOT) study was a prospective observational multicenter cohort study looking at the incidence, nature, and outcomes of severe critical events in the pediatric population across 33 centers in Europe, in children younger than 16 years of age undergoing elective or urgent anesthesia for diagnostic or surgical procedures [12]. In that study, the estimated incidence of severe perioperative critical events was 5.2%, with a 3.1% incidence of respiratory events and 1.9% incidence of cardiovascular events, with a resultant poor outcome in 5.4% of cases [12].

Most studies have highlighted respiratory complications as the primary cause of severe adverse outcomes following sedation or general anesthesia in children. Severe respiratory critical events include laryngospasm, bronchospasm, stridor, and bronchial aspiration. A history of prematurity increases the relative risk for the occurrence of these respiratory complications by a factor of almost two [12]. However, while the most frequently reported incidents are associated with the respiratory system (55%), cardiovascular events are the major causes of cardiac arrest (CA) [13] (Fig. 11.1).

In a large single-center study, the Risk Assessment of Morbidity in Pediatric Surgery (RAMPS) was developed and validated as a highly predictive comprehensive score of composite perioperative morbidity in infants and children undergoing noncardiac surgery. Using a five-component tool that includes patient's condition and surgical risk (Table 11.1), it provides an opportunity to improve perioperative planning, patient's outcomes, and resources allocation [14]. Similar to the APRICOT study, it reported a higher incidence of both respiratory and cardiac severe critical events in children up to 6 years of age [12].

The score includes the presence of critical illness, age < 5 years, ISR, and chronic condition indicator (CCI) [14]. The CCI is defined as a chronic condition that lasts ≥12 months and results in limitations in self-care, independent living, and social interactions, and/or need for ongoing medical interventions [14]. Alternatively, congenital conditions are also considered chronic in infants and neonates. The score ranges from 0 to 10, and provides an opportunity to improve perioperative planning and initiate pre-emptive interventions [14]. The risk of morbidity ranges from 1.8% (95% CI 1.6–2.0), for a score of 0 to 42.7% (95% CI 40.3–45.1) for a score of 10 [14]. (Fig. 11.2).

In addition, the RAMPS score provides good discriminatory ability in predicting the postoperative adverse outcomes of hypoxia (AUC = 0.733; 95% CI 0.658–0.809), transfer to higher level of care (AUC = 0.797; 95% CI 0.786–0.808), hemodynamic instability (AUC = 0.798; 95% CI 0.717–0.880), acute respiratory failure with need for intubation (AUC = 0.798; 95% CI 0.501–0.999), postoperative ICU ventilation (AUC = 0.831; 95% CI 0.817–0.844), acute neurologic decompensation (AUC = 0.848; 95% CI 0.776–0.921), and acute respiratory failure with need for noninvasive respiratory support (AUC = 0.848; 95% CI 0.785–0.911) [14].

11.2.2 Perioperative Mortality

Anesthesia-related death is rare, with an estimated risk of 0.1–1.2 per 100,000 anesthetics delivered for non-cardiac procedures [1–4]. Patients with significant life-threatening medical problems are at the highest risk with a 24-h mortality rate of 194 per 10,000 anesthetics and a 30-day mortality rate of 388 per 10,000 anesthetics, while the risk of anesthetic-related deaths in children without significant comorbidities is very low with a 24-h mortality rate of 0.2–22.6 per 10,000 anesthetics across multiple centers in the world [9].

CA is a well-established risk of anesthesia, surgery, and interventional procedures, with unexpected CA in the perioperative period being the most serious and disastrous complication in pediatric anesthesia [15, 16]. Large prospective multicenter registries of over 1.8 million anesthetic occurrences, including the Pediatric Perioperative CA (POCA) and the Wake Up Safe registries, have reported the incidence of perioperative CA in the general pediatric population to be in the range of 0.014–0.033%, with a mortality of 0.0036–0.011% [16, 17]. Respiratory and cardiovascular-related events accounted for most of all anesthesia-related CAs [18]. While some studies found cardiovascular causes to be more frequent than respiratory and medication-related causes [1, 19], other reports found respiratory causes of CA to be more frequent than the other two [1, 4, 20, 21].

The POCA Registry found that 49% of perioperative CAs in children were anesthesia-related, 75% of which occurred

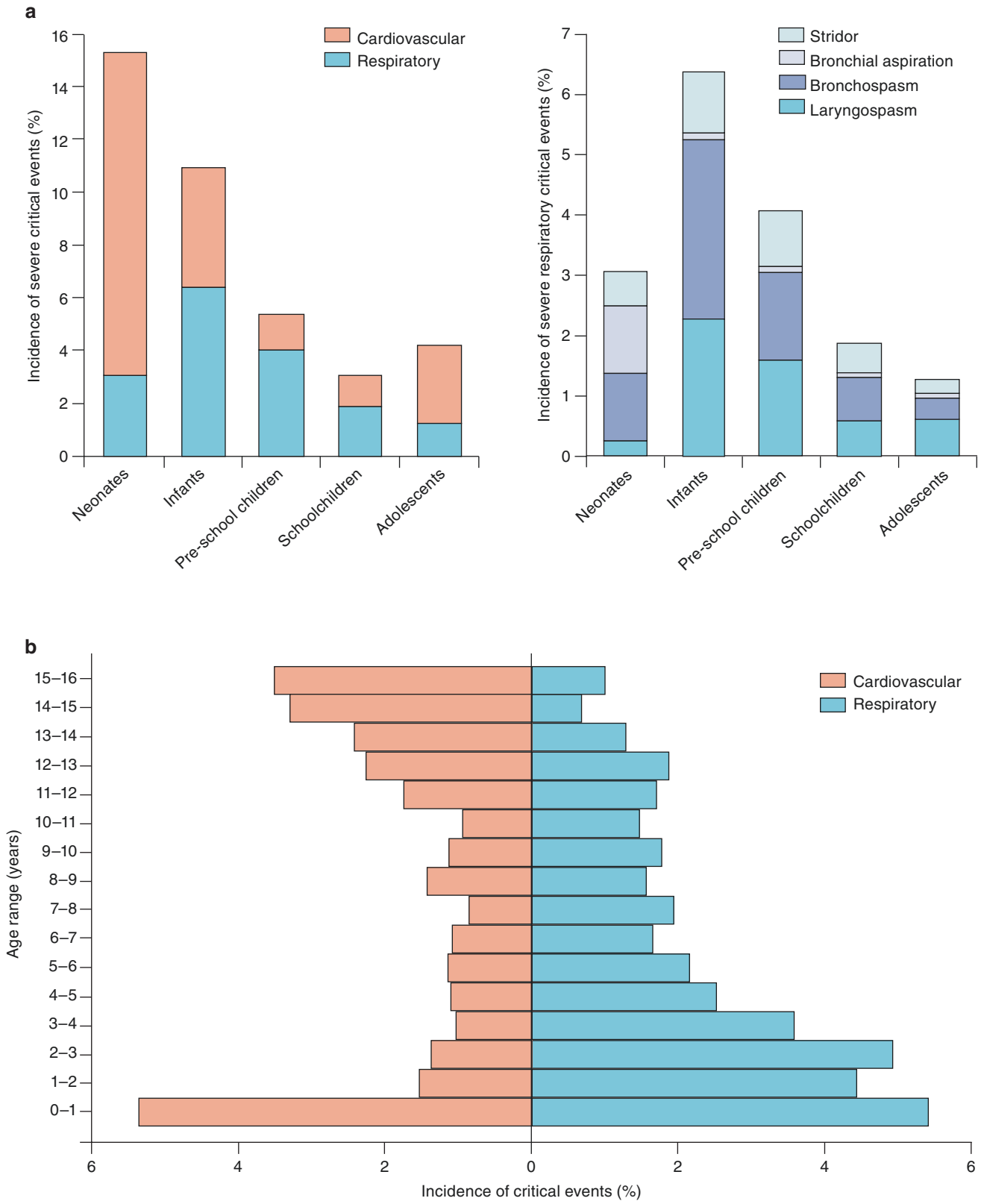

Fig. 11.1 Distribution of severe critical events throughout the age groups. (**a**) Relative incidence of respiratory and cardiovascular events (%), and relative distribution of the four respiratory critical events (%). (**b**) Age distribution of cardiovascular (orange) and respiratory (blue) critical events

in patients with an American Society of Anesthesiologists (ASA) physical status of 3–5, with cardiovascular causes accounting for the highest proportion of those arrests. Hypovolemia from blood loss and transfusion-related complications (e.g., hyperkalemia) were the most commonly identified cardiovascular causes [18, 19, 22, 23]. Respiratory events were responsible for 27% of all CAs, with airway obstruction from laryngospasm being the most common cause. Medication-related arrests accounted for 18% of all arrests, while the rest were due to other causes, such as equipment failure [19].

Most CAs (58%) occurred during maintenance of anesthesia, nearly one-quarter (24%) occurred in the preinduction or induction phase and 19% occurred during emergence, transport or recovery. The cause of arrest varied by phase of anesthesia care: 52% of arrests during anesthesia maintenance were cardiovascular in origin, while 50% of the arrests in the postoperative phase (emergence, transport, and recovery) were due to respiratory causes [19, 24]. There was a significant association between surgical procedure and cause of CA. As expected, respiratory events were the most common cause of arrest in patients undergoing airway surgery, while cardiovascular events were the most common cause of arrest in cardiac, neurosurgery, and spine surgery [19]. For instance, in cardiac surgery, there was a 42-fold increase in the odds of death compared to non-cardiac surgery [1]. Patients undergoing cardiac surgery had a higher 24-h mortality rate (127.1 per 10,000 anesthetics) and 30-day mortality rate (265.5 per 10,000 anesthetics) than did those undergoing noncardiac surgery (24-h mortality rate of 8.2 per 10,000 anesthetics and 30-day mortality rate of 24 per 10,000 anesthetics) [9]. The risk of severe critical cardiac events was significantly higher for surgical procedures compared to non-surgical procedures (mostly cardiac surgery and cardiac catheterization) with the child's physical condition preoperatively being an important determinant of morbidity [12]. Pulmonary hypertension (PH) was another major risk factor. A large study of more than 100,000 pediatric anesthetics found that 50% of all perioperative deaths occurred in patients with PH [9].

A number of studies have identified an increased risk of perioperative CA in neonates and children less than 1 year of age [4, 12, 13, 16, 19, 20]. Other major risk factors for CAs were emergency surgery and poor physical status [American Society of Anesthesiologists physical status (ASA-PS) ≥ III] [12]. For instance, mortality in ASA-PS III–IV patients was

Table 11.1 RAMPS score definition

Variable	Points
Age < 5 years	+1
Critically ill[a]	+1
CCI ≥3	+2
Significant CCI ≥2	+2
Intrinsic surgical risk quartile 3 or 4	+4

CCI chronic condition indicator, *RAMPS* risk assessment of morbidity in pediatric surgery
Significant CCI organs are cardiovascular, congenital, digestive, endocrine, genetic, neoplastic, neurologic, oral, respiratory, and urogenital
[a]Defined as the presence of any of the following characteristics of critical illness: preoperative mechanical ventilation, preoperative inotropic support, or preoperative cardiopulmonary resuscitation

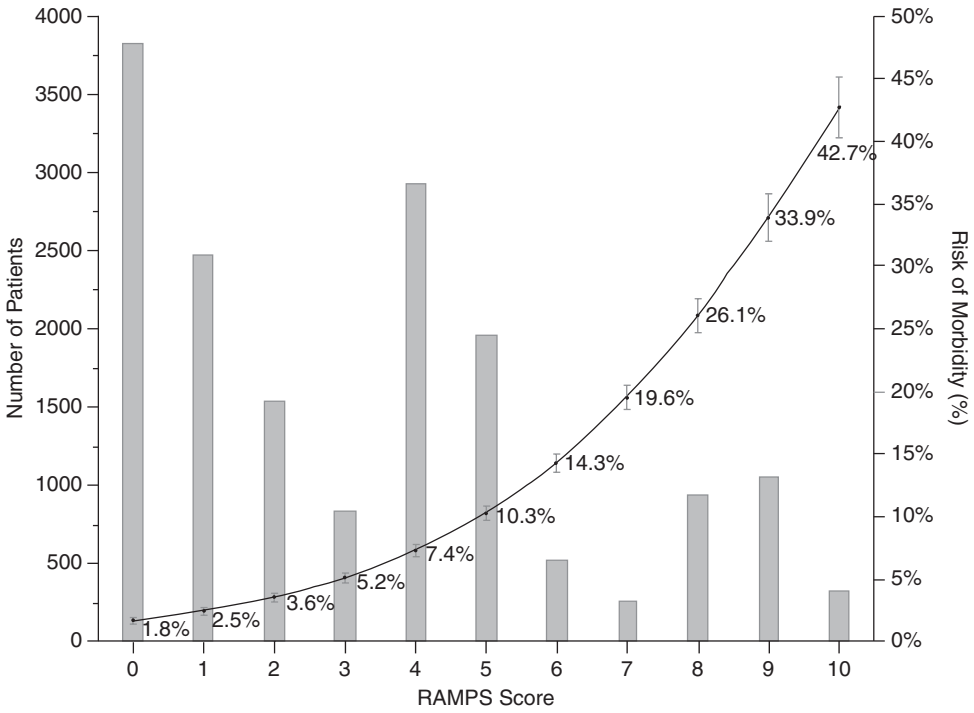

Fig. 11.2 Risk of the composite morbidity outcome as a function of the RAMPS score

found to be 37% compared with 4% in those with ASA-PS I–II, as these patients had fewer reserves and were less able to recover after hypoxemia or myocardial ischemia [1, 4, 13, 16, 19, 20, 25]. Survival rate of patients with anesthesia-related CA was 56% [18]. Additional risk factors were female gender and thoracic or upper abdominal surgeries [18].

11.2.3 Post-operative Adverse Events and Post-arrest Mortality

According to Wake Up Safe, which is a Pediatric Anesthesia Quality Improvement Initiative database that includes a multi-site voluntary registry of pediatric perioperative serious adverse events, 4.7% of pediatric perioperative cardiac arrest events occur in the Post-Operative Care Unit [24]. Similarly, the POCA Registry, found that approximately 20% of anesthesia-related pediatric CAs occur during emergence or recovery from anesthesia. During the post-operative period, children are at risk for serious physiologic compromise for many reasons, including the immediate post-surgical inflammatory phase, the residual effects of anesthetic and analgesic medications, and other possible underlying or unknown risk factors [19]. Both ASA physical status and emergency surgery have been reported as risk factors for anesthesia-related CA in children, as well as good predictors of mortality post-arrest. Mortality post-arrest was estimated at 26–28% in the first report from the POCA Registry [16].

11.3 Defining the Risk

The preoperative physical status of patients is determined using the ASA-PS classification. This classification is used worldwide by anesthesiologists and other health care providers in clinical practice and by researchers to characterize perioperative risk despite the fact that it was never intended to be a risk prediction tool [26, 27].

The simple classification system and ease of communication of an ASA-PS classification make the score practical to use, with low-risk patients being classified as ASA I or II and high-risk patients classified as ASA III or IV (Table 11.2). Although ASA-PS classification was not initially intended to grade the physical status of children, it has been widely adopted and has additionally been used to predict perioperative outcomes in children [28]. Studies have shown poor interrater variability among pediatric anesthesiologists when

Table 11.2 ASA-PS classification and pediatric examples

ASA-PS classification	Definition	Pediatric examples
ASA I	A normal healthy patient	No acute or chronic diseases, normal BMI percentile for age
ASA II	A patient with mild, well-controlled systemic or acute disease	Asymptomatic CHD, well-controlled dysrhythmias, asthma without exacerbation, non-insulin dependent DM, well-controlled epilepsy, abnormal BMI percentile for age, mild/moderate OSA, oncologic state in remission, autism with mild limitations
	No functional limitation	
ASA III	A patient with moderate to severe systemic or acute disease, that is not life threatening	Uncorrected CHD, asthma with exacerbation, poorly controlled epilepsy, insulin dependent DM, morbid obesity, malnutrition, severe OSA, oncologic state, renal failure, muscle dystrophy, cystic fibrosis, history of organ transplantation, brain/spinal cord malformation, symptomatic hydrocephalus, prematurity PCA <60 weeks, autism with severe limitations, metabolic disease, difficult airway, long-term parenteral nutrition
	Some functional limitation	
ASA IV	A patient with severe systemic disease or acute disease that is a constant threat to life	Symptomatic CHD, CHF, active sequalae of prematurity, acute hypoxic–ischemic encephalopathy, shock, sepsis, DIC, automatic implantable cardioverter–defibrillator, ventilator dependence, endocrinopathy, severe trauma, severe respiratory distress, advanced oncologic state
	Severe functional limitation	
ASA V	A moribund patient who is not expected to live beyond the 24 h without surgery	Massive trauma, intracranial hemorrhage with mass effect, patient requiring ECMO, respiratory failure or arrest, malignant HTN, decompensated CHF, hepatic encephalopathy, ischemic bowel or multiple organ/system dysfunction
ASA VI	A brain-dead patient whose organs are being removed with the intent of organ transplantation into another patient	
Addition of "E"	Emergency surgery	
	Delay in treatment will result in significant increase in threat to life or body part	

ASA-PS American society of Anesthesiologists physical status, *BMI* body mass index, *CHD* congenital heart disease, *DM* diabetes mellitus, *OSA* obstructive sleep apnea, *PCA* post-conceptual age, *CHF* congestive heart failure, *DIC* disseminated intravascular coagulation, *ECMO* extracorporeal membrane oxygenator, *HTN* hypertension

stratifying patients using ASA-PS [7, 28–30]. Being a subjective score, it does not include standardized criteria for defining comorbidities, and does not take into account the complexity of the surgical procedure performed [28, 31]. For instance, in the Aplin study, when consultant anesthesiologists that have been in practice for more than 5 years were given 15 hypothetical patient scenarios for ASA-PS grading, there was considerable inconsistency in the grading between raters, with 60% of the scenarios receiving at least three different gradings. The overall intraclass correlation coefficient (ICC) was found to be 0.447, indicating that 55% of the variance in ASA-PS gradings was due to measurement error in the ASA-PS, rather than true variance between respondents [28]. Ferrari et al. aimed to provide pediatric specific ASA-PS definitions with the intent of improving the consistency of assignments across providers. In this study, the same 15 cases used in the Aplin study were modified. Despite stratification by years of anesthesia practice, the overall ICC based on the modified ASA-PS definitions across all cases was only 0.58 [32]. The minimal improvement of ICC from 0.447 to 0.58 emphasizes the need for better tools to classify perioperative risk in pediatric patients [32].

During the past decade, risk stratification models have been developed for the pediatric surgical population to improve prediction of perioperative major events and enhance perioperative discussion of risk [7, 33]. For instance, the American College of Surgeons National Surgical Quality Improvement Program "ACS NSQIP" Pediatric Surgical Risk Calculator is one of the tools that are used to estimate the risk of perioperative complications and mortality [6]. It collects data on children that are less than 18 years of age undergoing non-cardiac procedures, and calculates the risk while taking into account concurrent patient comorbidities, preoperative risk factors, intraoperative characteristics, 30-day postoperative outcomes, and mortality in both the inpatient and outpatient settings as well as the type and acuity of the surgical procedure [34].

Due to the variability in risk assessment of the pediatric surgical patient, other risk scores have been developed and validated. The simplified Pediatric Risk Assessment (PRAm) scores was developed and validated using NSQIP Pediatric database and validated externally using a large sample from a quaternary care hospital [14, 30].

It has shown excellent accuracy in predicting perioperative mortality in neonates, infants, and children presenting for noncardiac surgery [7] (Table 11.3). It is a comprehensive score that takes into consideration patient characteristics, comorbidities, and the surgical procedure. Similar to the RAMPS score that targets morbidity, the PRAm score was developed and validated as a prediction tool of mortality, with critical illness being an important risk factor [14]. It includes age (e.g., less than 12 months), type of procedure (elective vs. urgent surgery), the presence of at least one comorbidity, critical illness, and neoplasm (Table 11.4) [7].

The PRAm score, being based on objective preoperative characteristics, had a better reproducibility with decreased interrater variability than the ASA-PS classification [7]. A score > 4 was associated with an exponential increase in

Table 11.4 List of patient's comorbidities and their clinical manifestations

Respiratory disease	Asthma, chronic lung or airway disease, cystic fibrosis, preoperative oxygen requirements, tracheostomy, preoperative mechanical ventilation, bronchopulmonary dysplasia *(preterm)*
Gastroenterological disease	Liver and pancreatic disease, diabetes, necrotizing enterocolitis *(preterm)*
Cardiac or congenital heart disease	Single ventricle physiology, valvular abnormalities, cardiac dysfunction, preoperative need of ionotropic support, preoperative cardiopulmonary resuscitation, pulmonary hypertension
Urologic disease	Acute or chronic kidney disease, need for dialysis
Neurologic disease	Mental retardation, cerebral palsy, central nervous system disease, seizure, intracerebral hemorrhage *(preterm)*
Hematologic–oncologic disease	Presence of a neoplasm, chemotherapy, preoperative transfusion[a]
Others	Immune disease, preoperative use of steroids

[a]Defined as transfusion of whole blood or red blood cells during the 48 h before surgery

Table 11.3 PRAm Score to predict postoperative mortality

Variables	Definition	Value
Urgent	Urgent surgical procedure	+1
Comorbidity	The presence of at least one comorbidity: Respiratory disease, congenital heart disease, preoperative acute or chronic kidney disease, neurologic disease, hematologic disease	+2
Critically ill	The presence of at least 1 of the following characteristics of critical illness: Preoperative mechanical ventilation, inotropic support, preoperative cardiopulmonary resuscitation	+3
Age < 12 months	Age at the time of the surgical procedure <12 months	+3
Neoplasm	Surgical procedure in a patient with a neoplasm with or without chemotherapy	+4

PRAm pediatric risk assessment

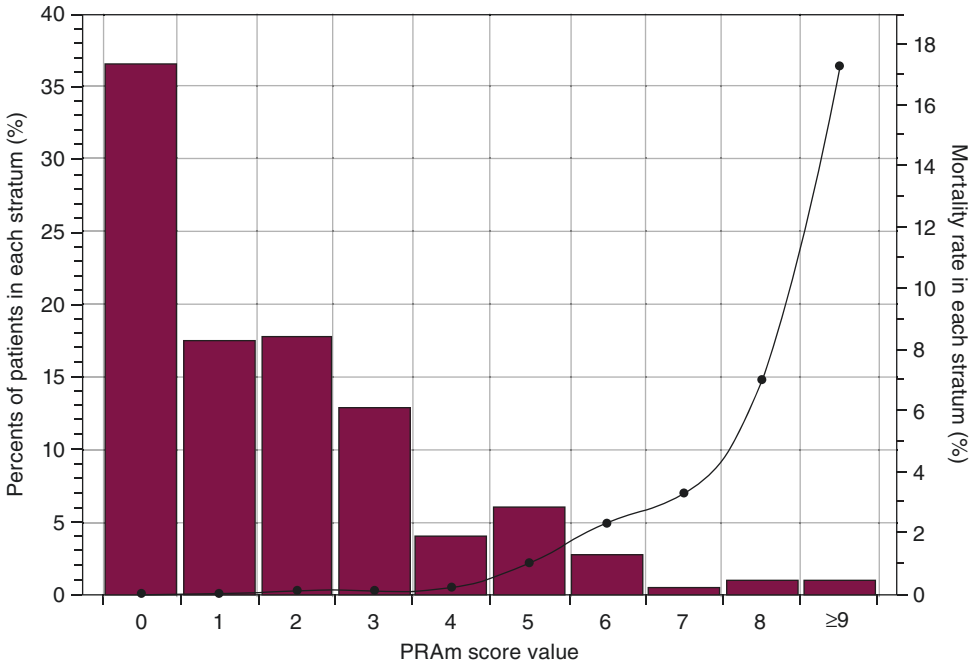

Fig. 11.3 Distribution of the Pediatric Risk Assessment (PRAm) score values in the derivation cohort (red bars) in relation to the observed in-hospital mortality rate (smoothed line) for each score

mortality rate (Fig. 11.3). The PRAm scoring system was found to be a more accurate and practical method to predict perioperative mortality risk in infants and children undergoing noncardiac procedures than ASA-PS scores. When compared to ASA-PS scoring system, there was a substantial variability in the PRAm scores for ASA-PS scores ≥IV. As such, patients with ASA-PS scores ≥ IV had PRAm scores ≤3 and, therefore, 22% of patients were incorrectly classified as high-risk patients. PRAm scores of ≥6 and ≤3 were identified as the optimal cutoff points for determining at which threshold a child's risk of mortality markedly increases and decreases, respectively [30].

The presence of comorbidities was also positively correlated with the predicted 30-day mortality risk. Among low-risk surgical procedures, mortality ranged from 0% with no comorbidities to 4.7% when all comorbidities were present. That risk was further magnified among high-risk surgical procedures, where mortality ranged from 0.07% when no comorbidities were present, to 46.72% when all comorbidities were present [8]. Non-survivors were more often neonates, with a low body weight (less than 5 kg), a higher ASA Physical Status classification (> III), higher rates of preoperative sepsis, needed inotropic support, had a congenital heart disease (CHD), or were ventilator dependent within 48 h preoperatively [8].

Perioperative mortality is strongly related to the interplay between the intrinsic operative risk and patient comorbidities. A patient with five comorbidities undergoing a low-risk procedure has a mortality rate of 4.7%, while a comparable patient has a mortality rate of 46.72% when undergoing a high-risk surgical procedure. In addition, an exponential

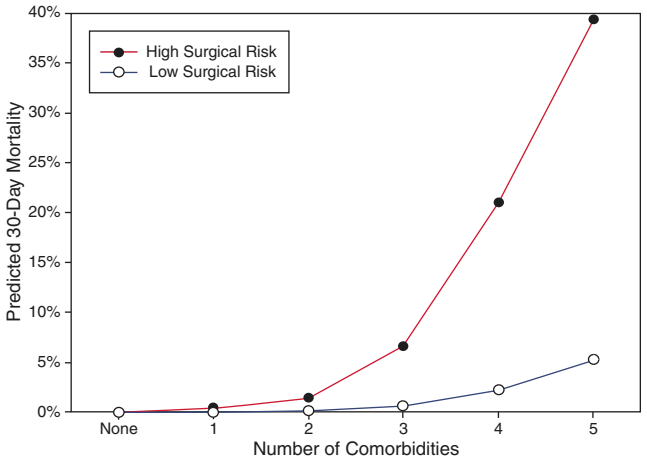

Fig. 11.4 Probability of 30-day mortality based on number of comorbidities

increase in mortality associated with each additional comorbidity above two was observed for procedures with high intrinsic risk [8] (Fig. 11.4).

11.4 The High-Risk Patient

11.4.1 The Premature, the Neonate, and the Infant

Neonates and infants have limited physiological reserve, and are at greater risk of complications with general anesthesia, with premature neonates being at the highest risk. With the

increased incidence of premature birth, more premature neonates are presenting for complex surgical procedures at an early age and are subjected to a higher risk of perioperative critical events [35]. Despite the medical advancement in perioperative neonatal care over the past two decades, the extremely premature infant is still at high risk of morbidity, mortality, and long-term neurodevelopmental disability [36, 37]. For instance, Lillehi et al., found the incidence of in-hospital mortality for noncardiac surgery to be five times higher in preterm than in full-term neonates (10.5% vs. 2%) [38]. Premature neonates undergoing abdominal surgeries during the first 2 months of life were found to have a high 30-day mortality risk and it increased significantly with progressive degrees of prematurity. That linear association might be explained by the fact that the most premature neonates were more likely to present with major comorbidities, such as necrotizing enterocolitis, sepsis, bronchopulmonary dysplasia (BPD), and severe intracranial hemorrhage, and have ionotropic requirements, or ventilator dependance [8, 36, 38, 39]. The neonatal research network reported overall survival to discharge rates for premature infants ranging from 33% in infants born at 23-week gestational age (GA) to 94% in those born at 28 weeks [36]. In addition, despite an observed increase in overall survival in infants born at 23–24 weeks, they were less likely to survive without major neonatal morbidity when compared to infants born at >25 weeks of gestation [36].

The unique physiology of neonates, the higher incidence of coexisting comorbidities, such as extreme prematurity, congenital malformations or heart disease, organ system immaturity, and an incomplete understanding of the pharmacology of the most commonly used anesthetics are among the several factors that are thought to increase their perioperative risk [40]. In neonates, perioperative alteration in physiologic parameters such as blood pressure (hypotension/hypertension), oxygen saturation (hypoxemia/hyperoxia), carbon dioxide (hypocapnia/hypercapnia), and blood sugar (hypoglycemia/hyperglycemia) can significantly affect postoperative outcomes and neurodevelopment [41–43].

The NEonate and Children audiT of Anaesthesia pRactice IN Europe (NECTARINE) study, a large European prospective multicenter observational study, studied neonates requiring anesthesia at less than 60-week postmenstrual age. A higher risk of perioperative critical events was seen, in preterm-born infants and in those that required preoperative intensive support, had concurrent co-morbidities or congenital anomalies, or had a longer surgical duration [44]. Critical events, such as hypotension (more than 30% decrease from baseline blood pressure), and hypoxemia (SpO_2 < 85%) requiring intervention, occurred in 35.2% of cases. Postmenstrual age was an essential determinant of morbidity, illustrating the age-specific vulnerability of neonates, with neonates younger than 28-week postmenstrual age being at the highest risk [44]. Intraoperative adverse events that would compromise tissue perfusion or oxygen delivery such as hypotension, hypoxemia, and/or anemia and requiring intervention were also shown to increase the 30-day mortality to 16.3% [44].

Postoperative apnea is another concern in extreme prematurity. It can be associated with airway obstruction, respiratory arrest, bradycardia, and possibly CA. Postoperative apnea can still occur in the absence of a preoperative history of apnea; with early apnea usually occurring in the post-anesthesia care unit (PACU), and late apnea occurring several hours later on the ward [45]. The incidence of postoperative apnea is inversely proportional to post-conceptual age (PCA) and GA, with most clinically relevant incidents occurring in infants <44-week PCA. Anemia (hematocrit < 30%) is an additional risk factors for postoperative apnea. Interestingly, the effect of anemia on apnea is most significant in infants on the older end of the age spectrum as the risk associated with young gestational and PCA decreases [45, 46]. The risk of apnea in preterm infants without anemia decreases to less than 5% at 48-week PCA with GA of 35 weeks or at a PCA of 50 weeks with GA of 32 weeks, but the probability of postoperative apnea does not decrease to less than 1% until the neonate has reached a PCA of 54 weeks with a GA of 35 weeks or PCA of 56 weeks with GA of 32 weeks [46].

General anesthesia (GA) is known to decrease upper airway muscle tone and may contribute to the development of apnea after anesthesia even in the absence of a history of apnea, and it can also induce or unmask abnormalities of the ventilatory control system. In a study comparing the rates of postoperative apnea between general and regional anesthesia (RA) in infants younger than 60 weeks postmenstrual age born older than 26 weeks of gestation undergoing inguinal herniorrhaphy, found that the incidence and severity of early apnea (0–30 min in PACU) was lower with regional anesthesia. It has also found a higher overall incidence of postoperative apnea in prematurely born (6.1%) than in full-term infants (0.3%), without a significant difference in late apneic episodes whether general or spinal anesthesia were used. However, among infants with postoperative apnea, the ones receiving general anesthesia were more likely to require interventions, such as manual stimulation, bag mask ventilation, and cardiopulmonary resuscitation (86% with GA vs. 50% with RA) [47].

Identifying infants at risk of apnea preoperatively may reduce postoperative morbidity and guide clinicians on the optimal age for surgery, type of anesthesia as well as the length and intensity of postoperative monitoring [47, 48].

11.4.2 The Patient with Congenital Heart Disease and Complex Syndromes

CHD and other congenital defects place neonates and infants at a higher anesthetic risk than older children and adults [18]. The incidence of moderate to severe CHD in the United States is estimated to be 6 per 1000 live-born, full-term infants [49]. With the recent advances in pediatric cardiology, surgery, and critical care, the survival rates of patients with CHD have improved and the prevalence of patients with CHD presenting for non-cardiac surgeries has increased [50, 51]. For instance, the Pediatric Health Information System database found that between 2004 and 2012, 41% of CHD children who had undergone corrective cardiac surgery in the first year of life, had also undergone at least one noncardiac surgery by the age 5 [52].

Children with major and severe CHD, as defined by poor functional status and residual lesion burden, have been shown to have an increased associated mortality when undergoing noncardiac procedures with 3.5 higher incidence of 30-day mortality when compared to children without CHD [33, 53, 54]. 6.5% of children undergoing noncardiac surgical procedures had a diagnosis of CHD. In patients who had at least 1 of the 100 most common noncardiac surgical procedures, 30-day mortality was 7.4% in the CHD cohort and 2.3% in children without CHD. Similarly, in another cohort, mortality was found to be 33% in patients with CHD as compared with 23% in those without CHD [55]. In infants <31 days, 30-day mortality was 13.3% in patients with CHD and 6.6% in infants without [53].

It is generally accepted that the risk of morbidity, CA and resultant mortality in patients with CHD undergoing noncardiac procedures is higher than in patient without CHD [1, 9, 53, 55]. The risk of mortality was found to be directly related to age, functional status at the time of surgery, the degree of underlying residual heart disease, and the anesthetic technique [50]. Forty-seven percent of CA occurs in children less than 6 months of age and 70% occurs in children less than 2 years of age [50]. Integration of ISR with comorbidities and severity of cardiac disease does not improve prediction of 30-day mortality in children undergoing noncardiac surgery. In children with CHD, patient comorbidities, and severity of the cardiac lesion are the predominant predictors of 30-day mortality [56]. The majority of CA is in patients who have either unrepaired (59%) or palliated (26%) defects. Single ventricle lesion patients are the most common group suffering CA with 70% of the arrests occurring in patients who are either pre-initial repair or pre-superior cavo-pulmonary anastomosis (SCPA) [53, 57, 58].

Previous studies have shown that the most common causes of unplanned hospital admission in CHD patients who presented for noncardiac procedures were cardiovascular (3.9%) and respiratory (1.8%) in nature [59]. The presence of major CHD, ASA-PS III, the performance of a recent echocardiogram, and procedures performed in radiology were identified as risk factors for postoperative admission with a 2.7% rate of unanticipated hospital admission [59].

In terms of complexity of the congenital heart defect, the NSQIP broadly classified CHD into minor, major, and severe (Table 11.5) [54]. That classification has been used to predict the likelihood of the occurrence of adverse events, such as CA, reintubation, infection, renal failure, neurological or thromboembolic complications, reoperation, 30-day unplanned re-admission, and 30-day prolonged hospital stay, and mortality in children less than 1 year [57].

Children with major and severe CHD undergoing noncardiac surgery have an increased risk of mortality, and a higher incidence of post-operative reintubation compared with matched controls undergoing comparable procedures [53]. There is a 2.3-fold increase in mortality in children with CHD compared to those without (2.8% vs. 1.2%). That mortality rate further increases to 3.9% in children with major CHD, and to 8.2% in children with severe CHD [54]. In another study the 30-day mortality was 11.3% in those with major CHD as compared to 5.9% in those with minor CHD [53].

Table 11.5 ACS NSQIP classification of congenital heart disease classification based on residual lesion burden on functional status

Classification of CHD	Definition and criteria
Minor	• Cardiac condition with or without medication and maintenance (e.g., ASD, small to moderate VSD without symptoms)
	• Repair of CHD with normal cardiovascular function and no medication
Major	• Repair of CHD with residual hemodynamic abnormality with or without medications (e.g., TOF with free PR, HLHS including stage 1 repair)
Severe	• Uncorrected cyanotic CHD
	• Patients with documented pulmonary hypertension
	• Patients with ventricular dysfunction requiring medication
	• Listed for heart transplant

ACS NSQIP American College of Surgeons National Surgical Quality Improvement Program, *CHD* congenital heart disease, *ASD* atrial septal defect, *VSD* ventricular septal defect, *TOF* tetralogy of Fallot, *PR* pulmonary regurgitation, *HLHS* hypoplastic left heart syndrome

11.4.2.1 The High-Risk Lesions

Single Ventricle Physiology

Multiple studies have found single ventricle physiology to be a risk factor for adverse events in patients undergoing noncardiac surgery. Hospital mortality rates among children with hypoplastic left heart syndrome presenting for noncardiac surgery are 17–22%. Several studies suggest that the highest risk period for these patients is before completion of the SCPA [58]. Specific anesthesia management guidelines are discussed in detail elsewhere [60].

Patients with Williams–Beuren Syndrome (WS) and Non-WS Elastin Arteriopathy

These patients are considered to be at high risk for anesthesia or sedation for multiple anatomic and physiological reasons. These patients characteristically have supravalvar aortic stenosis with an hourglass-shaped ascending aorta and central or peripheral pulmonary artery stenosis. Ventricular outflow tract obstruction leads to development of hypertrophy of the obstructed ventricle with bilateral outflow tract obstruction and biventricular hypertrophy uniformly recognized as a risk factor for sudden cardiovascular collapse under anesthesia/sedation. There are believed to be multiple sources of potential compromise of coronary blood, that alone or in combination, and lead to myocardial ischemia and cardiovascular collapse: (1) both ostial and diffuse left and right coronary artery stenoses may be present; (2) adhesion of the right or left aortic leaflet edge to the narrowed sinotubular junction can restrict coronary blood flow into the sinus of Valsalva; (3) loss of aortic distensibility results in a reduction in the diastolic component of phasic coronary blood flow; and (4) supply-demand imbalance that accompanies the development of concentric ventricular hypertrophy as seen with valvular aortic stenosis in the absence of coronary artery disease. Finally, prolongation of the corrected QT interval has been shown to be present in 13% of patients with WS and may contribute to the increased risk of sudden death [50, 61, 62].

Patients with Cardiomyopathy (Hypertrophic, Restrictive, and Dilated)

Hypertrophic cardiomyopathy's incidence is estimated at 0.24–0.47 per 100,000 per year. Patients have left ventricle (LV) hypertrophy, diastolic dysfunction, reduced LV compliance, left atrial enlargement, and increased left atrial pressure. LV contractility is generally preserved or hyperdynamic, but 5–10% of patients might develop LV hypertrophy, LV dilation, and reduced ejection fraction [63]. LV hypertrophy renders patients vulnerable to subendocardial ischemia and subsequent hemodynamic compromise from myocardial oxygen supply-demand imbalance. Mitral valve abnormalities are also characteristic, with the systolic anterior motion contributing to the dynamic LV outflow tract obstruction. In terms of hemodynamic monitoring under anesthesia, hypotension and tachycardia should be avoided as they might result in subendocardial perfusion and subsequent cardiovascular collapse [50].

Restrictive cardiomyopathy is a rare form of cardiomyopathy constituting around 5% of all pediatric cardiomyopathies. It is characterized by bi-atrial enlargement and severely restrictive biventricular physiology with normal systolic function and size [64].

Dilated cardiomyopathy (DCM) in children can have multiple etiologies. It can be idiopathic or secondary to genetic disorders, infection, drugs, CHD, or other medical conditions. DCM is characterized by ventricular dilation and impaired ventricular systolic function, loss of preload of recruitable stroke work, and exaggerated depression of stroke volume in the setting of elevated afterload [50]. Patients with DCM have been identified as a high-risk group in the POCA registry. Complications were common (38%) and occurred primarily (83%) in those with severe systemic ventricular dysfunction.

Patients with Ventricular Assist Devices

Currently, approximately 20–30% of pediatric patients awaiting heart transplant are bridged to cardiac transplant with a ventricular assist device. This has resulted in a 50% reduction in pediatric waitlist mortality [65]. Comprehensive discussion of the anesthesia and device management of pediatric patients supported with a ventricular assist device undergoing noncardiac surgery is beyond the scope of this chapter. Excellent comprehensive overviews of devices and their management are provided elsewhere [65, 66].

Association with Complex Genetic Syndromes

The association of genetic syndromes and congenital cardiac lesions is well-recognized [67]. In a large study of patients with CHD who underwent an anesthetic for surgical, interventional, or diagnostic cardiac procedures, 16.7% had at least one genetic syndrome, and 18.2% had an associated airway abnormality [68]. The most common genetic syndromes found among CHD patients were Down syndrome (6.0%), 22q11.2 microdeletion syndrome (3.6%), Stickler syndrome (3.0%), and CHARGE association (3.0%) [68].

Patients with genetic disorders often have multiple associated congenital anomalies, and present a unique challenge to the anesthesiologist [69]. Therefore, preoperative recognition and awareness of risk factors associated with specific genetic diseases is crucial to lessen the likelihood of perioperative complications [69]. Concerns range from metabolism of anesthetic drugs in patients with syndromes associated with renal or liver disease, to airway management in patients with dysmorphic features, to challenges related multiple

disease-specific features. For example, patients with muscular dystrophies or central cord disease are at risk of developing malignant hyperthermia [69]. Patients with Down syndrome and those with 22q11.2 microdeletion are known to have reactive airway disease, and airway anomalies that include laryngomalacia, tracheomalacia, tracheal bronchus, subglottic stenosis, and bronchomalacia [70–72]. The diversity of structural malformations, each with specific physiological perturbations, hemodynamic consequences, and severity, makes perioperative management of these patients quite challenging.

Consequently, children with CHD, particularly those with a residual lesion burden and compromised cardiovascular status, and patients with complex genetic syndromes require an individualized perioperative approach involving a multidisciplinary team with expert knowledge in the multiple aspects of the disease specific challenges [73].

11.4.3 The Patient with Pulmonary Hypertension

Pulmonary Hypertension (PH) is a heterogeneous and often progressive disorder that, when left untreated, can lead to right ventricular (RV) failure and death. The distribution of PH etiologies in children is different from that of the adult population. It includes a wide range of developmental pathologies, such as persistent PH of the newborn, congenital diaphragmatic hernia, pulmonary hypoplasia, BPD, CHD, and heritable syndromes or idiopathic pulmonary vascular diseases [74].

Historically, PH was arbitrarily defined as a resting mean pulmonary arterial pressure (mPAP) of ≥25 mmHg as measured with right-sided heart catheterization [75]. The Pediatric Taskforce of the sixth World Symposium on PH adopted the newly proposed adult definition for PH and further refined it for children to include those older than 3 months of age to account for the transient physiological elevation in pulmonary pressure that persists after birth. The currently adopted definition of PH from any cause in children >3 months of age is an mPAP >20 mmHg with a PVR index ≥ 3 Wood units (WU) · m^2 (PVR indexed to body surface area in children). Pulmonary arterial hypertension (PAH) or pre-capillary PH is defined hemodynamically by a mPAP ≥20 mmHg, pulmonary artery wedge pressure ≤15 mmHg, and indexed pulmonary vascular resistance >3 WU · m^2. Pulmonary arterial hypertension (PAH) after an SCPA is defined as a pulmonary transpulmonary gradient >6 mmHg (mPAP minus mean left atrial pressure) even if mPAP <20 mmHg [76].

Children with PH frequently present for diagnostic and therapeutic interventions related to their condition or for other surgical procedures (e.g., gastrostomy tube, tracheostomy, and ventriculoperitoneal shunt) and require general anesthesia [74, 77]. PH is known to put the child at an elevated risk of perioperative morbidity and mortality and at a higher risk of major perioperative complications, including CA and death. This associated perioperative risk has been consistently described in the literature and is thought to be positively correlated with the severity of the PH and the complexity of the surgical procedure [9, 77–79]. Thoracic procedures, including congenital diaphragmatic hernia repair, diaphragm plication, and video-assisted thoracoscopic surgery are among the procedures associated with the highest incidence of major adverse events [77]. Hence, children with PH are always considered by anesthesiologists, surgeons, and intensivists to be a high-risk patient population with a very challenging perioperative management [80].

Several single-center studies have reported that, in patients undergoing cardiac catheterization or non-cardiac surgeries, for the same procedure, the observed risk of CA is more than tenfold higher in children with PH than in patients without PH [79, 81]. Consistently identified risk factors include: systemic or supra-systemic PA pressures, evidence of syncope, elevated mPAP, moderate-to-severe RV dysfunction, younger age (<1 year), home oxygen requirements, and early stages of initiation of pulmonary vasodilator therapy [74, 77, 79, 82, 83]. Other important risk factors are ASA ≥ III, presence of a difficult airway, urgency and type of the procedure, degree of intraoperative hemodynamic lability and anesthetic management, degree of systemic inflammation response, and postoperative need for mechanical ventilation [74]. When 256 procedures performed in 156 patients (median age 4.0 years) in children with PH undergoing non-cardiac surgery or cardiac catheterization were reviewed, major complications, including CA and pulmonary hypertensive crisis, occurred in 4.5% of patients [82]. In an analysis of 77 children at a median age of 6 months with PH who underwent 148 non-cardiac procedures, major perioperative events included failed planned extubation (5.6%), postoperative CA (4.7%), induction or intraoperative CA (2%), and postoperative death (1.4%). Major events were more frequently seen in patients with severe baseline PH and in patients undergoing more complex surgeries. Preoperative inhaled nitric oxide and systemic vasodilator therapies were associated with a decreased incidence of minor but not major events, indicating that the preoperative use of pulmonary vasodilator therapy plays an important role in decreasing perioperative risk [77].

A large study of more than 100,000 pediatric anesthetics found that 50% of all perioperative deaths occurred in patients with PH [9]. Contrary to the relatively low previously documented risk of perioperative CA in the general pediatric population (0.014–0.033%, mortality of 0.0036–

0.011%), patients with PH had a higher rate of mortality and higher need for post-operative mechanical ventilation (0–3.5%) [16, 55, 77, 78, 84]. Moreover, according to data from over 50,000 children by the American College of Surgeons National Surgical Quality Improvement Program, reintubation rates were higher in children with PH than those without (5–5.4% vs. 1.7–2.3%) [34].

No single anesthetic is universally accepted for pediatric patients with PH; however, the main perioperative goal is a balanced anesthetic in order to avoid factors that might induce a PH crisis and the resultant RV failure (Table 11.6) [74].

An intraoperative PH crisis can be precipitated by a number of mechanisms, including noxious stimulus (e.g., intubation, airway suctioning, extubation, or surgical stimulation), discontinuation or interruption of pulmonary vasodilator therapy, or changes in intraoperative parameters. It usually manifests with signs of inadequate cardiac output and decreased pulmonary blood flow that are evident by an abrupt decline in the end-tidal carbon dioxide, bradycardia, and cardiovascular collapse. In the presence of an intracardiac right to left communication systemic, oxygen desaturation can be very rapid. In the event of an intraoperative PH crisis, the team must be aware of the immediate interventions to prevent cardiovascular collapse and those include ventilation with 100% oxygen, bronchodilator therapy to mitigate airway and bronchial hyperreactivity, optimization of anesthetic depth with adequate analgesia and neuromuscular blockade, administration of a fluid bolus in the setting of hypovolemia, ionotropic support of the RV, and reduction of RV afterload with inhaled nitric oxide [74].

In summary, in patients with PH, multidisciplinary perioperative preparation is crucial. Anesthesia should only be performed in these children when there is a sound clinical justification, and if anesthesia is necessary, and should be performed with great care to avoid precipitating a pulmonary hypertensive crisis. This is particularly important, because as actual procedure duration increases so does the risk of complications [85]. Moreover, since CA in these children can occur anywhere from induction of anesthesia to several days post-operatively, strong consideration for postoperative cardiopulmonary intensive care unit monitoring care is warranted [9, 77].

Table 11.6 Perioperative anesthetic goals for pediatric patients with PH

Avoid increased PVR: Avoid hypercarbia/acidosis/hypoxemia/hypothermia/high PEEP
Provide adequate anesthetic depth and analgesia to blunt sympathetic response to stress
Maintain preload, RV contractility and afterload
Maintain sinus rhythm and coronary perfusion

PVR pulmonary vascular resistance, *PEEP* positive end-expiratory pressure, *RV* right ventricle

11.4.4 The Patient with Respiratory or Airway Disease

Children frequently present for elective surgeries in the setting of an active or recent upper respiratory tract infection (URI). In children, the prevalence of URI ranges between 3% and 70% and can affect the upper, lower respiratory tract, or both [86, 87]. Viral invasion of the respiratory epithelium causes mucosal lining damage, airway smooth muscle activation, and results in increased sensitization of the airway to the irritant effects of anesthetic gases. Respiratory infections also increase secretions, ventilation–perfusion mismatch, elevate the closing volumes, and compromise diffusion capacity [87]. Anesthetic drugs and airway manipulation can further compromise an already sensitized respiratory system and might result in respiratory compromise. Careful preoperative optimization and perioperative monitoring are crucial to reduce perioperative respiratory adverse events and decrease morbidity in this patient population.

Patients with respiratory disease can present for surgery involving the airway or respiratory system or for other unrelated procedures. Respiratory complications during anesthesia can involve the upper, and/or lower airways and can have multiple clinical sequalae. Serious airway events are thought to commonly occur during induction of anesthesia, emergence from anesthesia, and in children with preexisting airway abnormalities. These include bronchospasm, laryngospasm, breath-holding, arterial desaturation, need for re-intubation, bacterial pneumonia, and unanticipated hospital admission [88]. Under anesthesia, the impairment of the ciliary apparatus responsible for clearing tracheal secretions coupled with the presence of an URI and the effect of anesthetics constitute cumulative factors that contribute to respiratory adverse events. Failure to recognize and treat airway obstruction, especially in younger children, can rapidly lead to oxygen desaturation and cardiovascular compromise. The POCA Registry found that 27% of reported CAs from 1998 to 2004 were respiratory related, and the majority were due to airway obstruction from laryngospasm [19].

Risks factors for respiratory severe clinical events include the presence of a sensitized airway in the setting of an acute or a chronic inflammatory process, prematurity, preoperative fever, signs of obstructive sleep apnea (OSA), ASA-PS > II, airway surgery and young age [12, 89]. It has been shown that younger patients, especially infants, have a higher incidence of airway complications [90]. Infants with an active URI and younger than 6 months of age had a higher incidence of bronchospasm than older children (20.8% vs. 4.7%). Children younger than 2 years of age had a higher incidence of oxygen desaturation than older children (21.5% vs. 12.5%) [21]. Other significant predictors of the risk of perioperative respiratory complications are parental confirmation of the child's URI symptoms, presence of nasal

secretions, passive smoke exposure, sputum production, and the presence of an underlying pulmonary disease [86, 91].

Children with upper airway disease, such as stridor, often require direct laryngoscopy or bronchoscopy in order to assess their airway for the presence of anatomical abnormalities. Airway obstruction might be due to fixed airway lesions, inflammatory, or infectious processes, and can manifest as difficulty with intubation, and/or extubation and an increased risk for acute respiratory distress [92].

Postponement of surgery for children with a history of a recent URI remains controversial. A decision to cancel surgery should take into consideration the amount of respiratory secretions during the acute illness, the coexistence of pulmonary disease, the requirement for intubation, and the surgical site involved, with airway, thorax, and upper abdomen being higher risks surgical sites [88]. Previous studies showed that URI-induced airway hyperreactivity can last several weeks, and increase the incidence of perioperative respiratory complications, and postponing elective surgery for at least 4–6 weeks was recommended [93, 94]. However, more recent studies have shown that URI rarely causes serious long-term complications. Comparison of children with active, recent, and no URI symptoms showed that despite a higher overall incidence of respiratory complications in patients with URI, the severity of adverse events was low, and most children had uneventful recoveries without any long-term adverse sequelae or deaths [21]. Most events respond to simple interventions, such as bronchodilators, continuous positive airway pressure (CPAP), endotracheal intubation, and short-term ventilation [88]. Moreover, the use of a laryngeal mask airway instead of tracheal intubation, and premedication with salbutamol or intravenous lidocaine, was shown to significantly reduce the incidence of perioperative respiratory complications in patients with a recent URI [95–97].

11.5 Conclusions

Improved survival from congenital conditions, as well as the introduction of new surgical techniques, has led to changes in the current practice of pediatric anesthesia. A significant proportion of patients presenting for surgery are premature and low birth-weight neonates with complex concurrent diseases and various congenital abnormalities. With the advancement in anesthetic, neonatal and intensive care, infants with younger GA and with multiple congenital anomalies or prematurity-related defects continue to frequently present for noncardiac procedures. Preoperative multidisciplinary care of this high-risk patient population, identification of risk factors and perioperative optimization can potentially decrease post-operative mortality and improve post-operative outcomes.

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