

and can vary between 6 and 14 Hz (Hz = 60 cycles/s). The amplitude of the ventilator is the distance the piston moves with each excursion, and by these excursions small breaths are propelled down the tubing. Several proposed mechanisms for the method of gas transport during HFOV have been proposed but none have been proven. Tidal volumes are dependent on the patient's compliance, ETT size, device frequency, and device amplitude. Tidal volume is inversely related to cyclic frequency:  $VCO_2 = \text{frequency} \times VT_2$ . Transitioning from conventional modes of ventilation to HFOV, the initial power setting ( $\Delta P/\text{amplitude}$ ) is adjusted to visible chest "wiggle" from the clavicles to the abdomen or pelvis. MAP ( $mP_{AW}$ ) is initially set approximately 5 cm H<sub>2</sub>O greater than the last  $mP_{AW}$  on conventional ventilation, just prior to the initiation of HFOV. Traditionally, tidal volumes in HFOV are considered to be just above FRC; however, it is difficult to measure actual tidal volumes and provide precise "optimal" lung volumes strategy. Clinically, MAP  $mP_{AW}$  is titrated by upward by 1 to 2 cm H<sub>2</sub>O till oxygenation improves, and inspired oxygen concentrations can be weaned to less toxic levels, below 0.60. While titrating  $mP_{AW}$ , it is important to assess for overdistention by following chest radiographs (CXR): overdistention/hyperinflation is determined by greater than nine posterior ribs or flattened hemi-diaphragms on CXR. Initial frequency settings, measured in Hz, can be found in **Table 79.7**. HFOV is the only mode of ventilation with active expiration. If hypercarbia, despite allowances for permissible hypercapnia, leads to profound respiratory acidosis and patient instability, minute ventilation can be improved by several means during HFOV. First, one of the drawbacks of HFOV is the lack of spontaneous ventilation and adequate airway clearance; therefore, inline suction (without breaking into the circuit causing derecruitment) should be used to ensure adequate airway, ETT patency, and lung recruitment. Second,  $\Delta P$  should be increased to maximize lung recruitment and increase minute ventilation. Third, frequency (Hz) can be slowly decreased to enhance lung recruitment and increase minute ventilation. Finally, the ETT cuff should be deflated to allow additional escape of CO<sub>2</sub> around the ETT. Disadvantages of HFOV include no partial ventilatory support leading to increased requirements for sedation and paralysis, cardiopulmonary interactions due higher  $mP_{AW}$  and decreased venous return, and loss of alveolar recruitment if circuit detached for suctioning of manual ventilation.

High frequency percussive ventilation (HFPV) pneumatically stacks subtidal volume breaths at a set rapid rate superimposed upon conventional cyclic rates. This allows

for a progressive stepwise inflation of the lung to a set peak pressure while allowing for passive exhalation to a preset lower pressure. HFPV has been well-described in the inhalational injury population for its ability to safely oxygenate and ventilate with continuous pneumatically-powered high frequency percussions to facilitate clearance of airway debris.<sup>360-362</sup> These properties may be particularly useful in pediatric patients with acute respiratory failure, by improving oxygenation and ventilation while maintaining lung protective strategies.<sup>363</sup>

## PEDIATRIC ACUTE RESPIRATORY DISTRESS SYNDROME

ARDS is a severe form of ALI that can result from a number of triggers that directly or indirectly injure the lung. The disease results in inflammation of the lungs, edema of the alveoli, and hypoxic respiratory failure. Prior definitions of pediatric ARDS (PARDS) often were adapted from studies on adult patients and adult consensus conferences. Although PARDS represents a small portion of PICU admissions, it is very clinically important as it carries a very high mortality rate. In turn, PARDS garners a significant amount of attention from PICU researchers and clinicians. Since 2012, PICU intensivists had been using the *Berlin definition* of ARDS<sup>364,365</sup> for management and study enrollment. Finally, in 2015 pediatrics had its own unique definition of ARDS. In 2015 the Pediatric Acute Lung Injury Consensus Conference (PALICC) completed their 2-year process of consensus meetings to provide a new definition of PARDS and guidelines for management.<sup>366</sup> The PALICC group included 27 experts from 8 countries. They used peer reviewed data that was specific to pediatrics to form new guidelines. Where data were unavailable specifically for pediatrics, recommendations were adapted from adult or neonatal data as appropriate. In areas where there was no available data, expert opinion formed the basis of their recommendations. Multiple follow-up publications have provided important information in PARDS, including methodology of the group,<sup>367</sup> the incidence and epidemiology,<sup>368</sup> comorbidities,<sup>369</sup> means of ventilator support,<sup>370</sup> noninvasive support,<sup>371</sup> monitoring,<sup>372</sup> use of ECMO,<sup>373</sup> and outcomes.<sup>374</sup> The group identifies the need for future randomized control trials in PARDS.

There are several key aspects to defining PARDS.<sup>375</sup> The PALICC definition of PARDS excludes neonates with perinatal-related lung disease, as it is likely a different entity. The lung injury should occur within 7 days of a known clinical insult. The hypoxic respiratory failure should not be able to be explained by cardiac failure or fluid overload. Chest radiographs typically have new infiltrates consistent with parenchymal lung disease. There are now separate sections for the use of noninvasive and invasive mechanical ventilation. One significant difference in comparison to adult ARDS definitions is that the definition of PARDS for mechanically ventilated patients includes stratification by oxygenation index or oxygen saturation index. Oxygenation index (OI) =  $[FiO_2 \times MAP \times 100]/PaO_2$ . The oxygen saturation index (OSI) =  $[FiO_2 \times MAP \times 100]/S_pO_2$ . Mild PARDS is  $4 \leq OI < 8$ , as well as  $5 \leq OSI < 7.5$ . Moderate PARDS is  $8 \leq OI < 16$ , as well as  $7.5 \leq OSI < 12.3$ . Severe PARDS is  $OI \geq 16$ , as well as  $OSI \geq 12.3$ . There is additional information for patients

**TABLE 79.7** Initial Frequency Settings in High-Frequency Oscillatory Ventilation

Patient Weight (kg)	Initial Frequency Setting (Hz)
<2	15
2-15	10
16-20	8
21-30	7
31-50	6
>50	5

with cyanotic heart disease, chronic lung disease, and left ventricular dysfunction. Future studies will need to address these more difficult aspects of defining PARDS.

The management of mechanical ventilation in PARDS currently can be summarized as the use of restrictive tidal volumes, increased use of PEEP, an ongoing relative tolerance of hypoxemia as long as it does not alter systemic oxygen delivery, and a tolerance of relative hypercarbia to reduce trauma from elevated mechanic ventilator pressures. The PALICC group among many others recognizes that there has never been a randomized control trial of tidal volume restriction in PARDS. There are also prior studies that have demonstrated a lower mortality with larger tidal volumes in pediatric patients.<sup>376,377</sup> This seems to be a result of the increased use of pressure control ventilation in pediatric patients. An individual patient might be sick enough to be classified as having ARDS, but those with a milder form of the disease have better pulmonary compliance. As pressure is set on the ventilator, larger tidal volumes occur with better compliance. The PALICC guidelines do not make a recommendation as the mode of ventilation. However, the guidelines do recommend targeting the delivered tidal volume to be “in or below the range of physiologic tidal volumes for age/body weight (i.e., 5-8 mL/kg predicted body weight) according to lung pathology and respiratory system compliance.”<sup>366</sup> It should be noted that PALICC guidelines do recommend adjusting the tidal volumes to the degree of disease severity. They recommend tidal volumes of 3 to 6 mL/kg predicted body weight for those patients with poor respiratory system compliance. They do believe the larger tidal volumes could be appropriate for patients with better pulmonary compliance.

Potentially, one of the more important recommendations from the PALICC group has been the increased application of PEEP. They recommended levels of PEEP of 10 to 15 cm H<sub>2</sub>O for patients with severe PARDS and identify that levels higher than 15 cmH<sub>2</sub>O may be needed for some patients. Given concerns for the potential cardiopulmonary interactions, they do recommend following hemodynamics closely. The application of increased PEEP may have significant importance in future PARDS studies. It has recently been shown by Khemani et al.<sup>377</sup> that the use of PEEP settings lower than those recommended by the ARDS Network Protocol is associated with increased mortality in PARDS.

Some by extrapolation would consider the use of HFOV the most extreme form of tidal volume restriction. HFOV is able to prevent atelectasis by maintaining a constant airway pressure. Trauma from lung stretch is avoided by delivering tidal volumes that are less than anatomic dead space.<sup>378</sup> Unfortunately, there is very little information in pediatric mechanical ventilation with no recent randomized control trials. There have been two recent adult studies, but they did not yield results supportive of HFOV. OSCAR<sup>357</sup> was a negative study, and OSCILLATE<sup>379</sup> was stopped early for a potential increase in mortality in the HFOV group. Adult practitioners are likely moving away from HFOV and use in pediatrics remains regionalized to a few centers that continue its use. The PALICC guidelines leave HFOV as a potential rescue therapy.

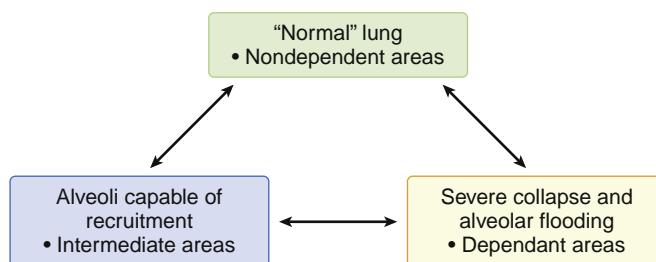
There are further adjunctive therapies for PARDS that will require future studies to confirm their potential benefit. This list would include the use of corticosteroids, inhaled

nitric oxide, ECMO, prone positioning, use of neuromuscular blockade, and the use of exogenous surfactant. There is insufficient data at this time to state these therapies should be routinely used for PARDS. Inhaled NO should be used for patients who have documented pulmonary hypertension or right heart dysfunction. The most recent published pediatric study of inhaled NO shows the possibility for harm.<sup>380</sup> The use of extracorporeal life support for PARDS has not been sufficiently studied to indicate it is beneficial. Further, given the complexity of the therapy, future trials may be very difficult, and to what extent ECMO is used for PARDS will vary based upon the individual institution.

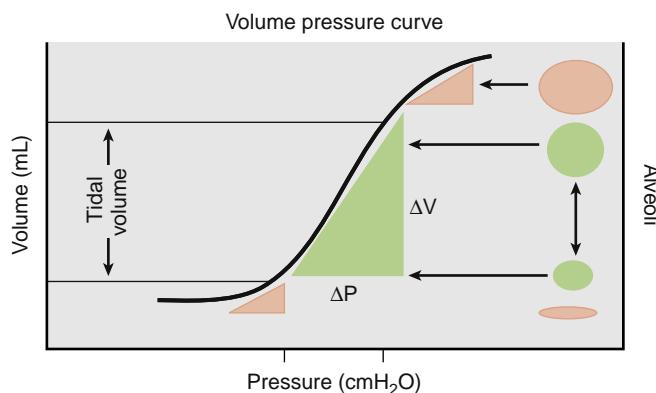
As patients progress through their disease course and care is no longer increasing, the issue of weaning from mechanical ventilation and timing of extubation must be addressed. Various different strategies have been used to wean off of the ventilator to varying degrees of success. Likely one of the most effective strategies is the daily scheduled use of spontaneous breathing trials (SBTs) to assess whether a patient is ready for extubation.<sup>381,382</sup> Faustino et al. in 2018 published a secondary analysis of the RESTORE clinical trial.<sup>383</sup> Of patients requiring mechanical ventilation for lower respiratory tract disease, they found 43% passed their first extubation readiness. Of the group that passed an extubation readiness test, 66% were extubated within 10 hours. Many PICUs are using protocols to provide daily SBTs. In the right setting, the breathing trial can be performed safely by the respiratory therapy staff without physician input. In the near future, we will see an increase in computerized ventilation protocols driving care in the PICU. Without protocols, there is significant variability in usual care mechanical ventilation strategies,<sup>384</sup> and even with protocols, there can be poor adherence to protocols.<sup>385</sup> As a group, PICU intensivists would benefit from computer decision support and likely would accept some version of this.<sup>386,387</sup> Future studies will be needed to determine if we can find the Goldilocks version of ventilation protocols. We need to provide not so little mechanical ventilation that the patient is struggling to breathe. Yet, we must provide not so much that there is atrophy of the diaphragm.<sup>388,389</sup>

## PRINCIPLES OF LUNG PROTECTIVE STRATEGIES: LIMITING VENTILATOR ASSOCIATED LUNG INJURY

As lung injury progresses, in response to pulmonary or extrapulmonary injury, the lungs can be divided into three hypothetical regions: (1) areas with severe collapse and alveolar flooding “dependent areas”; (2) recruitable areas with alveolar atelectasis “intermediate areas”; and (3) normal lung “nondependent areas” (Fig. 79.4). The goal of mechanical ventilation is to recruit intermediate areas, allowing improved gas exchange, spare normal areas of lung from ventilator associated lung injury (VALI), while giving dependent collapsed regions of lung with alveolar flooding time to recover from the primary process resolves (i.e., pneumonia, sepsis, etc.). Lung recruitment of intermediate areas and prevention of VALI is accomplished by using PEEP and limiting tidal volume and plateau pressures. This can be a complicated task, so let us first look at Fig. 79.5, and try to conceptualize a theoretical pressure-volume curve of the lung. As alveolar airway pressure increases, there is



**Fig. 79.4** For the purposes of lung protective ventilator strategies, the lung can be divided into three hypothetical areas.



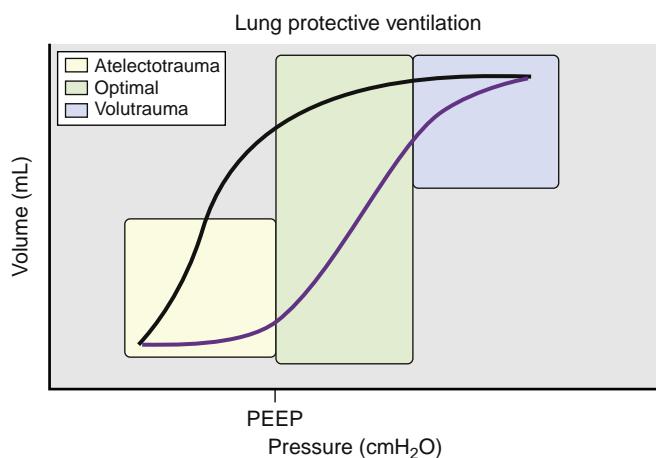
**Fig. 79.5** Volume pressure curve.

an opening pressure ( $P_{flex}$ ) required to overcome airway resistance and alveolar compliance (Compliance =  $\Delta V/\Delta P$ ). Pressures below  $P_{flex}$  will lead to alveolar collapse, termed *atelectasis*. If airway pressure cycles above and below  $P_{flex}$ , alveoli will continually open and collapse, leading to wall shear stress and eventual damage: *atelectrauma*. Following the hysteresis curve to the upper extent of the inspiratory limb, as pressure increases, there comes a point termed,  $P_{max}$ , whereby the alveoli start to become overdistended. Above  $P_{max}$ , shear stress again leads to alveolar damage, this time termed *volutrauma*. Therefore, in theory, we attempt to keep tidal volumes on the most compliant part of the volume-pressure curve, above  $P_{flex}$  and below  $P_{max}$ , leading to the idea called “open lung ventilation.” Triggered by the ARDSnet’s initial study, the use of low tidal volumes (6–8 mL/kg) with the addition of PEEP (open lung strategy) may reduce morbidity and mortality in patients with ARDS (Fig. 79.6).<sup>390</sup> However, as lung injury to the normal and intermediate areas of the lungs progresses, the volume-pressure curve moves to the right as the compliance of the lungs decreases, leaving a smaller therapeutic window requiring an increase in PEEP, resulting in higher MAP to maintain recruitment of areas of normal and recruitable lung (Fig. 79.7).

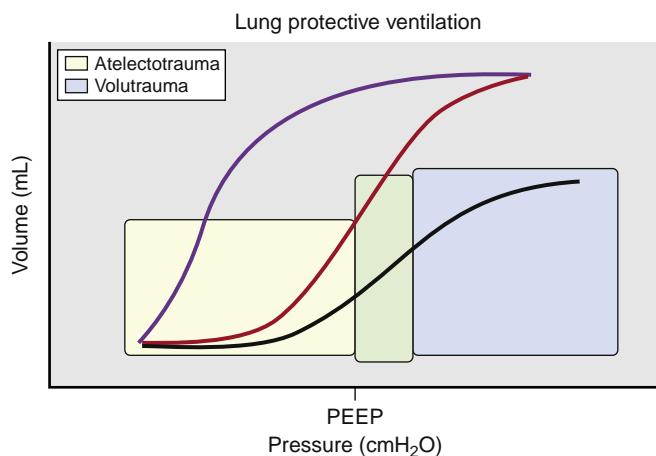
Lung protective strategy attempts to decrease *VALI* by inhibiting volutrauma, barotrauma, atelectrauma, oxygen toxicity, and biotrauma (Fig. 79.8).

**Low Tidal Volume:** Despite using usual control groups in the ARDSnet original study, employing a low tidal volume approach of 6 to 8 mL/kg has become a standard of care.

**PEEP:** The advantages of PEEP as a distending pressure include: increase in FRC, improvement of respiratory

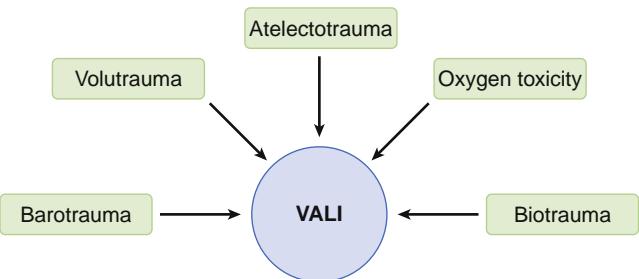


**Fig. 79.6** Lung protective ventilation strategy. *PEEP*, Positive end-expiratory pressure.



**Fig. 79.7** Lung protective ventilation with worsening lung compliance. *PEEP*, Positive end-expiratory pressure.

#### Ventilator Associated Lung Injury (VALI) lung protective ventilation strategy



**Fig. 79.8** Tenets of ventilator-associated lung injury. *VALI*, Ventilator associated lung injury.

compliance, improvement of ventilation/perfusion mismatch, redistribution of lung water/edema. PEEP ultimately improves arterial oxygenation. The use of low tidal volumes has been consistent across multiple recent trials, but the selection of PEEP in these trials has been highly variable. Recent pediatric studies have shown that setting PEEP lower than the ARDSnet guidelines can result in increased mortality.<sup>391</sup> Further, guidelines from

the PALICC recommends increased levels of PEEP.<sup>366</sup> It can be difficult to determine the critical opening pressure of alveoli clinically. Therefore, most clinicians initially use a minimal distension strategy by setting PEEP between 5 and 9 cm H<sub>2</sub>O, as lung injury progresses and hypoxemia worsens, PEEP may be increased to increase mean plateau pressures (keep <30-35 cm H<sub>2</sub>O) and aid in recruitment. More precise methods of determining optimal PEEP in patients with ARDS include titration using dynamic compliance or static pressure-volume loops to identifying the critical opening pressure. Alternatively, one can use titration with dynamic compliance or static pressure-volume curve. Likely, in the future we will determine optimal PEEP in patients with ARDS use transpulmonary pressures with an esophageal catheter. It is important to remember that as PEEP is increased and lung is recruited, intrathoracic pressure is also increased. There has been concern by clinicians that increased intrathoracic pressure can inhibit cardiac output by reducing venous return. There have been a number of studies that have shown even with increasing PEEP there is not a decrease in cardiac output.<sup>392,393</sup> However, given the concern for decreased cardiac output, hemodynamics should be monitored as PEEP is increased.

**Plateau Airway Pressures:** Sustained plateau airway pressures greater than 35 cm H<sub>2</sub>O can lead to barotrauma: pneumothorax, pneumomediastinum, and subcutaneous emphysema. In an attempt to limit barotrauma, PaCO<sub>2</sub> is allowed to increase in the face of inadequate minute ventilation. This permissible hypercapnia can be employed as long as the patient tolerates the acidosis and is able to buffer with the renal retention of HCO<sub>3</sub> and there are no contraindications from coexisting disease.

**Driving Pressure:** Driving pressure is the peak inspiratory pressure minus the PEEP for patients who are paralyzed and receiving mechanical ventilation. Amato et al.<sup>394</sup> demonstrated in a reanalysis of adult ARDS patients involved in prior randomized trials that decreases in driving pressure due to changes in ventilator management were strongly associated with increased survival.

**Neuromuscular Blockade:** Neuromuscular blocking agents (NMBAs) have been provided to patients with ARDS to control ventilation and reduce trauma caused by increased tidal volume or increased airway pressure. NMBAs may also allow patients to tolerate higher levels of PEEP. This would lead to decreased trauma from repeated opening and closing of lung units. Further, NMBAs may reduce oxygen consumption from both skeletal and respiratory muscles. Papazian et al.<sup>395</sup> as part of the ACURASYS study demonstrated that early use of NMBA improved the adjusted 90-day survival with ARDS and increased the time off of the ventilator. They did not see an increase in muscle weakness with the use of cisatracurium. Pediatric trials looking at use of NMBAs have not yet been performed.

## ADJUVANT THERAPIES FOR ACUTE RESPIRATORY DISTRESS SYNDROME

### Prone Positioning

In pediatric patients, Curley et al.<sup>396</sup> demonstrated that prone positioning was associated with an improvement in oxygenation in patients with ARDS. This group also showed

proning can be safely applied in pediatric patients.<sup>397</sup> However, proning was not associated with a benefit in mortality or ventilator-free days, and the trial was stopped early for futility.<sup>396</sup> Prone positioning improves lung recruitment in select patients with ARDS. This may explain the difference between adult and pediatric results. In adults, Guerin et al.<sup>398</sup> performed a multicenter prospective randomized control trial, Proning Severe ARDS Patients (PROSEVA), which showed that early administration of prone positioning significantly decreased 28-day and 90-day mortality. Between these two studies, the pediatric patients were more heterogeneous and the adults were homogenous with more severe ARDS. The impact of patient selection and duration of prone positioning is unclear; however, it is likely that a subgroup of patients, respond to prone positioning early after lung injury, and immediate responders may benefit from prolonged prone positioning.<sup>399</sup> Pediatric patients with brain injury and worsening hypoxemia prone positioning may be attempted with careful monitoring of ICP.<sup>400,401</sup> Future studies in pediatrics are needed.

### Surfactant Therapy

Exogenous surfactant therapy is standard of care in neonates suffering from RDS; however, the utility of surfactant therapy in the treatment of ALI and ARDS is uncertain and continues to be researched. In pediatric patients, a 2003 study by Möller et al.<sup>402</sup> showed immediate improvement in oxygenation and a trend toward improved survival with the exogenous surfactant therapy, calfactant. However, Willson et al. in a recent randomized control trial found that surfactant did not improve oxygenation and decrease mortality relative to placebo administration.<sup>403</sup> However, there was no difference in length of mechanical ventilation or ICU stay. The current PALICC guidelines do not recommend routine use of surfactant.<sup>366</sup> Clinicians still feel that there still may be a specific pediatric patient population (i.e., near drowning victims) that still may benefit from exogenous surfactant administration, and research is ongoing to determine patient selection, timing, and combination with other therapies for treatment of ALI/ARDS.

### Corticosteroids

A great percentage of pediatric patients with ARDS will receive corticosteroids at some point during their hospitalization. There are a number of underlying issues of inflammation and potentially adrenal insufficiency that would prompt clinicians to provide them. There were two pediatric studies published in 2015 that provide some insight. Drago et al.<sup>404</sup> published a small randomized placebo controlled trial of 35 patients with ARDS. There was no difference between groups with regard to duration of mechanical ventilation, length of ICU stay or mortality. They did find that it was feasible to provide low dose infusions of methylprednisolone without significant increases in nosocomial infections or serum glucose. Yehya et al.<sup>405</sup> reported a single center observational study in which 169 of 283 children with pediatric ARDS received corticosteroids for greater than 24 hours while receiving mechanical ventilation. The group that received steroids had fewer ventilator-free days and a longer duration of mechanical ventilation in survivors. Currently, the PALICC guidelines do not recommend routine therapy with corticosteroids for pediatric ARDS.<sup>366</sup>

## Nitric Oxide

Inhaled nitric oxide (iNO) acts as a selective pulmonary vasodilator to improve V/Q mismatch, decrease pulmonary hypertension, and reduce right ventricular cardiac work. NO upregulates cGMP, ultimately resulting in smooth muscle relaxation and pulmonary arteriolar vasodilatation. iNO is delivered directly to ventilated lung units and improves perfusion in these areas of lung without significant effects on the rest of the pulmonary vascular bed, thereby improving V/Q mismatch and oxygenation in patients with ARDS. Much like prone positioning and surfactant therapy, NO can result in transient improvements in oxygenation. A systematic review and meta-analysis performed by Adhikari et al.<sup>406</sup> in adults with ARDS showed inhaled NO does not reduce mortality, regardless of severity of illness. In pediatrics, a small, randomized trial by Bronicki et al.<sup>407</sup> showed that pediatric patients with ARDS randomized to receive iNO had significantly improved ECMO-free survival and ventilator-free days at 28 days. This trial only had 55 total subjects and did not show a difference in overall mortality. The most recent study was a propensity matched cohort of 499 pediatric patients with ARDS by Bhalla et al.<sup>380</sup> There were a total of 143 that received iNO. They found that use of iNO was not associated with improvement in ventilator-free days or mortality. There still remains a role for iNO in patients with pulmonary hypertension, right heart dysfunction, and potentially a bridge to ECMO. Any further roles would require future studies to show benefit.

## Extracorporeal Membrane Oxygenation

ECMO remains a rescue strategy for pediatric patients with ARDS that fail to respond to advanced modes of mechanical ventilation. There has been much more research with ECMO in adult ARDS as compared with pediatrics. The CESAR Trial in adults demonstrated improved outcomes in adults treated with ECMO; however, this trial had significant methodological flaws.<sup>408</sup> Results of the EOLIA (ECMO to rescue lung injury in severe ARDS) were reported in 2018.<sup>409</sup> The trial enrolled adults with very severe ARDS. They found that 60 day mortality was not significantly lower in the group randomized to ECMO as compared with conventional mechanical ventilation and possible use of ECMO as a rescue therapy. With regard to pediatric data, in 2018 Barbaro et al.<sup>410</sup> published a secondary propensity score matching analysis of ECMO use in patients from the RESTORE study. They found that in patients with severe pediatric ARDS there was not superior outcomes in the group treated with ECMO as compared with those that did not receive ECMO support. With improved care and research, presumably the mortality risk for both ECMO as well as ARDS will decrease. J. C. Lin<sup>411</sup> recently published a review on this topic which may provide additional insights. Further research regarding ECMO support of severe pediatric ARDS is needed.

## ADJUNCTIVE PHARMACOLOGIC THERAPY: SEDATIVES AND ANALGESICS

Sedation is often required to help children cooperate with mechanical ventilation. The amount of sedation required depends on the child's age, size, underlying disease, and amount of respiratory support needed. Some children are neurologically depressed and require no sedation. Sedation allows patients to breathe "in phase" with the ventilator,

which reduces the peak airway pressure and eliminates coughing and straining, all of which can cause pulmonary gas leaks or inadequate ventilation. Sedation has changed over the past many years in PICUs across the country. Part of the cause of this can be attributed to the development of protocols to limit sedation to decrease tolerance, withdrawal symptoms when sedation was weaned, and the potential for exacerbation of delirium. Many of the larger PICUs participated in the RESTORE study.<sup>359</sup> The RESTORE study can serve as a good example of how to deliver sedation using protocols. Each patient's level of sedation was titrated to a State Behavioral Scale, which allowed for a common language among care providers.<sup>412</sup> The medications that they used to provide sedation while patients were intubated were primarily morphine and midazolam. They recommended the use of fentanyl infusions as the opioid agent for patients that had hypotension or reactive airways disease. There were also secondary sedation agents that were used which included pentobarbital, ketamine, methadone, clonidine, dexmedetomidine, and propofol. Some institutions did use lorazepam as an alternative benzodiazepine. Pentobarbital and ketamine were adjunct medications when the patient was unresponsive or less responsive to the primary agents. Methadone and clonidine were adjuncts used primarily to prevent withdrawal symptoms as the patient was tapered off medications. Dexmedetomidine and propofol were used in this study as temporary agents to wean off other medications in anticipation of extubation. Propofol is not used in some units or only used as a temporary measure because of the concerns for propofol infusion syndrome.<sup>413</sup> Dexmedetomidine is seeing increased usage in PICUs across the country not just for short-term sedation. In some instances, it can replace opioids as a means of providing sedation. There should be a word of caution in administering lorazepam to premature neonates. Lorazepam repeatedly dosed over several days may cause steroid-responsive hypotension as a result of buildup of drug in the body. The half-life of lorazepam is approximately 72 hours in premature infants. Giving the drug every 4 to 6 hours causes accumulation of the drug in blood and tissues.

NMBAs increase chest wall compliance, reduce oxygen consumption, and facilitate mechanical ventilation. If neuromuscular blocking drugs are used, they should be administered in conjunction with medications that cause amnesia and anxiolysis and control pain. Vecuronium, rocuronium, and cisatracurium are the most commonly administered muscle relaxants used in the PICU (also see Chapter 27). Rocuronium is often given for intubation and for intermittent dosing. Vecuronium can be used as an intermittent agent but also as a continuous infusion. There are risks of decreased metabolism and prolonged clearance with vecuronium infusions and many will choose instead to use cisatracurium. Cisatracurium is often useful because its elimination is not dependent on renal or hepatic function. If these drugs are given for more than a day, provision of regular drug holidays should be considered to avoid serum buildup of the drug and prolonged paralysis.

## WEANING FROM MECHANICAL VENTILATION

The pediatric literature falls behind adult publications with regard to guidance in weaning and extubation from mechanical ventilation. A 2009 review by Newth et al.<sup>414</sup>

addressed what was known at the time. Attempts have been made to develop predictive indices identifying which children can be successfully weaned from mechanical ventilation. Most of the indices are used in research but do have clinical applications. One indices is the Rapid Shallow Breathing Index (RSBI) from Yang and Tobin.<sup>415</sup> The RSBI is equal to the RR/tidal volume. When patients are breathing comfortably, they have a lower RR with larger tidal volumes. In this circumstance, the RSBI is a low number. Further, patients with respiratory distress tend to breathe more rapidly with smaller tidal volumes and hence have a higher RSBI. There are several different techniques for weaning from mechanical ventilation. These include lowering the set ventilator rate over time, performing a daily SBT, or increasing pressure support or CPAP sprints.<sup>416</sup> Many hospitals are initiating daily SBTs for their patients. These are periods of decreased ventilatory support while the patient is observed for evidence of respiratory distress. The decreased support can be pressure support, CPAP, or T-piece ventilation. Patients are observed to see that there is no significant increase in RR, decrease in saturations, diaphoresis, hemodynamic compromise, or evidence of increased work of breathing. The successful completion of a SBT will initiate of plans for extubation. Depending on the ICU, SBT are carried out under direction of the physicians or they can be independently performed by the respiratory therapist. It is possible that computerized weaning protocols will further reduce time on mechanical ventilation.<sup>417</sup> At the moment it seems that the best solution is to ask on a daily basis whether the patient is able to be extubated. Studies indicate a significant percentage of patients being evaluated for weaning are ready for extubation.<sup>418</sup>

We must keep in mind that as we are weaning patients from mechanical ventilation, there is an anticipated extubation failure rate. If we continue mechanical ventilation until we are absolutely certain a patient will not fail, many patients will be ventilated longer than necessary. A 2003 review<sup>418</sup> of 16 ICUs showed an extubation failure rate of 6.2% (range 1.5%-8.8%) for patients requiring mechanical ventilation longer than 48 hours. Our own research shows a reintubation rate of 8.3% following extubation.<sup>286</sup>

With regard to the degree of decreased ventilatory support during an SBT, use of CPAP does not put patients under increased stress. Multiple prior studies demonstrate that infants or children with smaller ETTs are not “breathing through a straw” when put on CPAP or T-piece.<sup>419-422</sup> Relative to an adult, the ETT may be smaller in diameter, but it is also shorter and the inspiratory flow rate in infants is low compared with an adult. Flow rates are measured to be approximately 0.5 L/kg/min.<sup>421</sup> Therefore, a 3 kg infant has a flow velocity of 1.5 L/min as compared with 30 L/min for a 60 kg adult. If patients are unable to successfully complete an SBT, it is possible they would not manage the work of breathing postextubation.

Overall, the criteria for extubation readiness includes intact airway reflexes, hemodynamic stability, manageable secretions, and an appropriate level of alertness. The amount of negative inspiratory force (NIF) the patient can generate can be measured. A NIF should be measured with a calibrated manometer and inspiration from residual volume. Typically, a NIF of negative 30 or more is associated with extubation success. The presence of a leak around the ETT may be supportive of extubation. There is some

research showing the absence of a leak around the ETT does not predict extubation failure.<sup>423,424</sup> However, absence of a leak is associated with the development of subglottic upper airway obstruction after extubation.<sup>286</sup> Extubation failure is typically defined as reintubation less than 24 hours after a scheduled extubation attempt. Extubation failure may be caused by a multitude of reasons but large category is postextubation upper airway obstruction. We believe the incidence of upper airway obstruction to be between 37% and 41%.<sup>286,418</sup> As there is significant interobserver variability<sup>286</sup> in the clinical assessment of upper airway obstruction, physiology based tools may be valuable.<sup>286</sup> Objective measures of airway obstruction may be necessary before we have a definitive answer as to which therapies reduce subglottic narrowing and reduce obstruction.

## RESPIRATORY DISORDERS

### Laryngotracheobronchitis (Croup)

Croup occurs most frequently in the 3-month-old to 3-year-old age group. Croup is a viral infection (parainfluenza, influenza, adenovirus) that causes edema of the tissues in the upper airway, particularly in the immediate subglottic region. There is usually a history of a few days of upper respiratory tract infection symptoms followed by hoarseness, a croupy cough, and possibly stridor. The degree of respiratory distress and the child's ability to compensate for the increased work of breathing are best assessed clinically. These patients are initially treated with mist and aerosolized racemic epinephrine to reduce swelling of upper airway mucosa.<sup>425</sup> Steroid administration is common yet controversial.<sup>87</sup> Tracheal intubation is required when the child can no longer sustain the increased work of breathing and CO<sub>2</sub> increases. When the trachea is intubated, the ETT should be 0.5 to 1.0 mm smaller than usual for age. The ETT must be of sufficient size that the patient can breathe easily during spontaneous ventilation and the nurses can effectively suction secretions from the airways. Croup usually resolves spontaneously in 3 to 7 days. The average duration of tracheal intubation is approximately 5 days. Laryngotracheobronchitis is less common in children older than 4 years.

### Epiglottitis

Epiglottitis is an inflammation of the mucosa of the supraglottic structures that was previously caused by *Haemophilus influenzae* type B but is now commonly caused by *Staphylococcus aureus* and streptococcal organisms because immunization against the *Haemophilus* organism has been so effective. In the past, epiglottitis was a disease of 4- to 6-year-old children. Now, it occurs more commonly at older ages (even in adults).<sup>426</sup> In young children, epiglottitis is a true airway emergency because it may rapidly progress to complete and fatal airway obstruction. Providing a secure airway is the first priority. Children with epiglottitis appear toxic and have a fulminant onset of fever and respiratory distress. Tracheal intubation during anesthesia is commonly required until antibiotic therapy (ampicillin and chloramphenicol or ceftriaxone) is initiated and the signs of systemic toxicity subside. Introduction of the *H. influenzae* vaccine has dramatically decreased the incidence of *H. influenzae* infection, as well as that of other *H. influenzae* processes.<sup>131</sup>

## Bronchiolitis

Bronchiolitis is an acute viral infection of the lower respiratory tract that occurs primarily during the first 2 years of life. The signs and symptoms of this malady are air trapping, wheezing, mild to moderate systemic hypoxemia, increased work of breathing, and increased airway resistance. The cause is usually an infection with respiratory syncytial virus (RSV).<sup>427</sup> Patients at high risk for respiratory failure from this disease include infants and young children with a history of prematurity, chronic lung disease, or congenital heart disease. Apnea is frequently the first sign of decompensation in neonates, which often occurs before significant hypercapnia appears. Fatigue is a common indication for mechanical ventilation. Treatment is primarily supportive and includes endotracheal intubation and mechanical ventilation for respiratory failure.<sup>428</sup> RSV immune globulin (RespiGam) is a prophylactic IV drug that is administered to patients at risk for seasonal RSV disease (ex-premature infants, infants with congenital heart disease, immunosuppressed patients, or those with multiple congenital anomalies); it has dramatically decreased the incidence of illness in this population. Ribavirin is a virostatic drug available for the treatment of children with RSV and congenital heart disease, immunosuppressive disease, or multiple congenital anomalies.

## Cystic Fibrosis

Cystic fibrosis is a fatal autosomal recessive disease carried on chromosome 7. Although it affects the pancreatic, hepatic, pulmonary, GI, and reproductive systems, 90% of the reported morbidity and mortality is pulmonary.<sup>142</sup> The pulmonary pathology consists of severe airway obstruction, bronchiectasis, emphysema, and terminal respiratory failure.

Survival of patients with cystic fibrosis has improved dramatically over the past 30 years. More than one-third of patients survive to greater than 30 years of age.<sup>143</sup> This change is the result of improved antibiotic therapy, nutritional support, and aggressive treatment of complications. Lung transplantation has been performed in patients with chronic respiratory failure with varied success.<sup>429,430</sup>

## Bronchopulmonary Dysplasia

BPD is a form of chronic lung disease that occurs in patients who have survived severe neonatal lung disease. The cause of this disease is uncertain, but usually patients were premature, had hyaline membrane disease, and required prolonged and aggressive respiratory support with high inflating and distending pressure and high oxygen concentrations. Inflammation appears to be an important component of this disease.<sup>431</sup> Children with BPD have decreased dynamic compliance, increased airway resistance, increased physiologic dead space, and markedly increased work of breathing. The lungs are hyperinflated, and there are intercostal retractions, nasal flaring, and wheezing. Chest radiographs demonstrate large lung volumes and fibrosis as well as cystic and atelectatic areas. Hypercapnia and hypoxia are present to varying degrees.<sup>432,433</sup> Therapy for BPD includes providing enough calories to meet the higher energy expenditure required for the increased work of breathing. Respiratory support (mechanical ventilation, CPAP) is required for some patients. Diuretics and bronchodilators

are frequently used and may be associated with electrolyte abnormalities. Most long-term survivors have subjectively normal pulmonary function. However, some survivors have severe chronic physiologic changes.<sup>434,435</sup> During the first years of life, viral or bacterial pulmonary infections often increase the need for respiratory support; these infections may prove to be fatal. Great effort is being made to prevent BPD. Because the trauma of mechanical ventilation on an immature lung is thought to be the major cause of BPD, alternative modes of ventilatory support are being evaluated, including exogenous surfactant, high-frequency ventilation (especially HFOV),<sup>436</sup> ECMO, and liquid ventilation.<sup>432,437</sup>

## Sleep Apnea

Normal ventilation during sleep requires normal upper airway anatomy and normal intact reflexes. The latter include central responses to hypercapnia and hypoxia, response to airway irritation, and dynamic phasic contraction of the pharyngeal and hypopharyngeal muscles. Sleep apnea usually occurs when one or more of these protective responses is abnormal. In infancy, sleep apnea is relatively common. Numerous causes have been postulated, the most attractive of which is immaturity of the medullary chemoreceptors. Patients with Ondine's curse, the most severe form of central apnea, have complete apnea when asleep. Lesser breathing disorders may be present during sleep in patients with sudden infant death syndrome. Treatment of sleep apnea consists of respiratory stimulants (theophylline), cardiorespiratory monitoring during sleep, and in some severe cases, tracheotomy and nighttime mechanical ventilation. Obstructive sleep apnea occurs in all pediatric age groups. It may be associated with an identifiable anatomic disorder, such as enlarged tonsils and adenoids, the Pierre Robin syndrome, and tracheal and laryngeal malacia. Signs and symptoms of obstructive sleep apnea include loud snoring, obstructive episodes with frequent arousal, behavior disorders caused by sleep deprivation, and cor pulmonale. The diagnosis is made by the history, ECG, and formal sleep studies. Bronchoscopy may also be helpful in defining the problem. In young children, an enlarged liver may suggest that the child has pulmonary hypertension. Treatment of sleep apnea includes removal or bypass of an obstruction. Although tonsillectomy and adenoidectomy may improve the airway, there may still be significant airway obstruction for the first few days after surgery. Rarely does such a child require a tracheostomy.

## Foreign Body Aspiration

Foreign body aspiration is a relatively common and often catastrophic event in children. Although it can occur at any age, the peak incidence of foreign body aspiration occurs at 6 months to 3 years of age. Vegetable matter (peanuts) and other foodstuff (hot dogs) or coins and small pieces of toys are the most commonly aspirated material. Many of these objects are radiolucent. The symptoms of aspiration are related to the location of the foreign body within the airway and the time since the object was aspirated. Acute symptoms may include total airway obstruction, stridor, wheezing, or acute onset of coughing, whereas more chronic symptoms include bloody sputum, chronic coughing, or wheezing. The diagnosis of a foreign body in

the airway is made from the history and physical examination and, in some cases, by radiologic imaging. The efficacy and safety of abdominal thrusts have been questioned. The Heimlich maneuver and back slaps are reserved for acute upper airway obstruction with no air movement. Treatment of less acute or lower airway foreign body aspiration includes bronchoscopy, postural drainage, chest physical therapy, bronchodilators, and surgical removal of the object.<sup>438</sup>

### Upper Airway Obstruction and Meningomyelocele

Vocal cord paralysis is a common result of several disorders, including brainstem abnormalities and myelodysplasia. Children with meningomyelocele usually have an Arnold-Chiari malformation and may have stridor. This lesion allows caudal displacement of the medulla, stretching of the cranial nerve tracts, and abnormal arterial architecture of the brainstem. Vocal cord paralysis may result from pressure on the brainstem (i.e., with hydrocephalus) or from focal infarcts of the brainstem. Treatment of these brainstem abnormalities includes relief of the hydrocephalus and, if the paralysis persists, cervical decompression of the Arnold-Chiari lesion. Despite these surgical procedures, some children require a tracheotomy and long-term mechanical ventilation.

## ASTHMA

The prevalence of childhood asthma is increasing over time. Estimates from the Centers for Disease Control and Prevention placed the percentage of children with asthma at 3.6% in 1980 5.8% in 2003 and 9.5% in 2011 ([www.cdc.gov/nchs/fastats/asthma.htm](http://www.cdc.gov/nchs/fastats/asthma.htm)). Thankfully, the majority of children with asthma will never require intensive care. However, for the children that do there can be significant morbidity and a risk of mortality. In a 2012 study by Newth et al.<sup>439</sup> of fatal and near-fatal asthma in an ICU setting, 12% of patients had complications and the mortality was 4%. Cardiac arrest prior to admission occurred in 10 of the 11 patients who died. For the purposes of this section critical asthma is defined as an asthma exacerbation requiring ICU admission.

Asthma is a disease of inflammation. There is infiltration of the submucosal area of the airways with mast cells, eosinophils and CD4 lymphocytes. Degranulation of mast cells releases leukotrienes and histamine causing edema, increases in mucus production, and chemotaxis of white blood cells (WBCs). Multiple factors can trigger an asthma attack and degranulations of mast cells. Such factors include allergens, infections (viral > bacterial), changes in the weather, and strong emotions. Inflammation increases irritability of the airway as well as airway hyper responsiveness. The airway lumen is decreased by spasm of the bronchial muscles, edema, and mucus. Decreases in the airway lumen significantly increase airway resistance. For laminar airflow, airway resistance is related to the third power of the radius, but with turbulent airflow it is related to the fourth power. Due to the smaller lumen of their airways, children experience much greater changes in airway resistance during asthma attacks than adults. Due to resistance in exhalation, an expiratory wheeze is typically noted. Bronchospasm, edema, or mucus plugging

can lead to complete obstruction of small airways. Hypoxemia occurs as a result of a mismatch in ventilation and perfusion. Airway dead space is increased by obstruction of the airways. To maintain ventilation, the RR is typically increased. In turn, the initial PaCO<sub>2</sub> is usually low. Respiratory fatigue or impending failure may be identified by a normal or elevated PaCO<sub>2</sub>.

It should be reinforced early that wheezing is caused more things than just asthma and that asthma can occur without wheezing. Wheezing is the sound that is produced when there is obstruction to airflow. Wheezing can be caused by pneumonia, upper airway obstruction, foreign body aspiration, and CHF. Each would require different therapy. Wheezing in a toddler of a sudden onset should prompt evaluation for foreign body aspiration. The history should be addressed at recent choking or coughing episodes. Even the presence of a history of reactive airways or atopy does not rule out aspiration. A high index of suspicion should be maintained. Intermittently a chest-ray obtained for a child who is wheezing shows cardiomegaly rather than peribronchial cuffing. Asthma is statistically more likely but this can be the presentation of heart failure. In turn, a chest x-ray is warranted for any patient with their first presentation of wheezing patient and certainly for any child who is admitted to the ICU for wheezing. With regard to asthma that occurs without wheezing, the movement of air is required to hear wheezing. It is possible to have such significant airflow restrictions that patients don't produce audible wheezing. Patients who present with a quiet chest or limited airflow on auscultation require immediate action.

Children presenting with an asthma exacerbation may have a few days of URI symptoms followed by increased work of breathing. The patient may have low room air oxygen saturations. The patient's position of comfort may be sitting up to support their muscles of respiration. Accessory muscle use is noted. There is a prolonged expiratory phase on auscultation. Some children in an effort to increase airway pressure may be breathing out with pursed lips or in smaller children grunting may be noted. The child may not be able to speak in more than one or two word phrases. Therapy should be started immediately first with supplemental oxygen to address hypoxemia. If the child mild respiratory distress, nasal cannula oxygen may be sufficient. If the child has moderate or severe respiratory distress, oxygen should be delivered by either face mask or non-rebreather face mask. Inhaled beta agonists such as albuterol are given to relax bronchial smooth muscles. IV or subcutaneous terbutaline or epinephrine may be required if there is not enough air movement to deliver inhaled medications. Steroids should be given early as the effect will take some time. If there is limited improvement with initial therapy arrangements should be made for ICU admission. Many emergency departments will attempt to obtain arterial blood gases. However, the clinical picture alone may provide enough information to guide therapy.

### Asthma Therapy

**Supplemental Oxygen.** Oxygen can be delivered with a standard nasal cannula, but the FiO<sub>2</sub> is limited. Standard nasal cannula might provide up to 28% FiO<sub>2</sub>. Increasing the flow of oxygen with a standard cannula above 4 to 5 LPM

is not usually tolerated. A simple face mask might increase the  $\text{FiO}_2$  to 50%. A tightly sealed non-rebreather face masks might be able to provide a  $\text{FiO}_2$  closer to 1. Providing oxygen with a HFNC may provide nearly complete humidification of the airway gases and the  $\text{FiO}_2$  also approaches 1. A 2014 study by Rubin et al.<sup>440</sup> demonstrated a decrease in effort of breathing in patients receiving HFHNC. The mechanism of its effect is not elucidated. Some clinicians have begun using HFHNC as a mechanism for delivery of beta agonists or other aerosolized medications, but there is not yet data supporting its use.

**Inhaled  $\beta$  Agonists.** Inhaled  $\beta$  agonists are used to relax bronchial smooth muscles. The most commonly used  $\beta$  agonists is albuterol, which is a racemic mixture of the active R and inactive S enantiomer. Levalbuterol, the active R enantiomer, is available as a separate preparation, but recent studies have not shown it to be more effective<sup>441</sup> or have less elevations in HR.<sup>442</sup> Albuterol is  $\beta_2$  selective and comes as a metered dose inhaler or solution for nebulization. For initial therapy in the ICU, continuous albuterol is preferred, and the usual dose is 0.15 to 0.5 mg/kg/h or 10 to 20 mg/h. After improvement in air movement with decreased respiratory distress, intermittent doses can be given every 1 to 2 hours. Terbutaline as an inhaled medication is less  $\beta_2$  selective compared with albuterol and therefore is used less commonly. Terbutaline remains as an important IV medication. Tachycardia is commonly associated with albuterol use. At times it is unclear if the elevated HR is related to toxicity of medications or due to ongoing respiratory distress. Arrhythmias may be seen with albuterol use but this is usually just an increased frequency of PVC. Diastolic hypotension is observed with higher doses of albuterol, although this can be related to decreased intravascular volume and increased intrathoracic pressure. Agitation and tremors can be seen with CNS stimulation. Hypokalemia may be noted as the Beta agonists drive potassium into cells. Ipratropium bromide, an inhaled anticholinergic, is sometimes paired with intermittent albuterol doses. Ipratropium bromide has the benefit of promoting bronchodilation without decreasing mucociliary clearance.

**Corticosteroids.** IV steroids are preferred to oral dosing in the ICU due to the possibility of decreased absorption or delayed onset. Methylprednisolone is used commonly due to its limited mineralocorticoid effects. The initial dose is 2 mg/kg and then 0.5 to 1 mg/kg every 6 hours. There may be regional preference for dexamethasone or hydrocortisone. Steroids are typically given for the duration of the acute asthma phase. If steroids are given for 5 days or less, they are not usually tapered. Systemic steroid use is associated with hyperglycemia, hypertension and occasionally agitation. In the initial ICU care inhaled steroids are of no benefit.

**Intravenous Fluids.** Children admitted to the ICU with critical asthma will likely be dehydrated from limited oral intake during their illness and increased insensible losses from the higher RR. The patient's circulating volume should be supported with fluid boluses if needed. However, excessive fluids should be avoided as this could lead to pulmonary edema. Pulmonary edema could worsen both

oxygenation and airway resistance. Fluid boluses may also be needed for children whose respiratory distress progresses require mechanical ventilation. Hypotension often occurs during intubation.

**Intravenous and Subcutaneous  $\beta$  Agonists.** A significant decrease in air exchange may result in poor delivery of inhaled medications and IV  $\beta$  agonists may be required. Terbutaline is often the first choice of the available beta agonists. Terbutaline is relatively  $\beta_2$  selective as compared with isoproterenol and epinephrine. Terbutaline can be given subcutaneously for children without IV access as a dose of 0.01 mg/kg/dose up to a maximum of 0.3 mg. IV terbutaline is loaded at a dose of 10  $\mu\text{g}/\text{kg}$  over 10 to 20 minutes followed by a continuous infusion of terbutaline in a range of 0.1 to 10  $\mu\text{g}/\text{kg}/\text{min}$ . The infusion can be titrated to effect. Subcutaneous epinephrine may be given for severe asthma exacerbation with limited IV access with a dose of 0.01 mg/kg of to the 1:1000 solution with a maximum dose of 0.5 mg. Absorption of the drug may be limited by poor perfusion to extremities. IV epinephrine may be an ideal drug for mechanically ventilated patients with hypotension. The use of isoproterenol in critical asthma has decreased over time.

**Methylxanthines.** There is regional variation in the use of the methylxanthine aminophylline in place of IV terbutaline as a second line drug for critical asthma. Fewer children with asthma are admitted to the ICU with a methylxanthine as a chronic medication. There are improved controller medications including the leukotriene inhibitors so fewer children are receiving oral theophylline. The methylxanthines promote bronchial smooth muscle relaxation, but the exact mechanism of action is not known. IV aminophylline is loaded at a dose of 5 to 7 mg/kg over 30 minutes, followed by a continuous infusion in the range of 0.5 to 0.9 mg/kg/h. If the patient has taken oral theophylline in the past 24 hours, the loading dose is reduced by 50% or the aminophylline dosing is adjusted based on a serum theophylline level. In general, an aminophylline loading dose of 1 mg/kg will raise the serum theophylline level by 2  $\mu\text{g}/\text{mL}$ . The target range for serum theophylline in acute asthma is 10 to 20  $\mu\text{g}/\text{mL}$ . Theophylline has a very narrow therapeutic window. Theophylline levels above 20  $\mu\text{g}/\text{mL}$  are associated with nausea, tachycardia, restlessness, or irritability. Higher theophylline levels have been associated with seizure activity.

**Magnesium.** Magnesium can be given as an inhaled or IV medication to relax bronchial muscles. Smooth muscle relaxation occurs due to magnesium's effect as a calcium channel blocker. Results from the 2013 MAGNEsium Trial in Children (MAGNETIC)<sup>443</sup> indicate nebulized magnesium may be beneficial in an acute severe asthma exacerbation. There is some evidence that IV magnesium may also be beneficial in severe asthma.<sup>444,445</sup> As there is still regional variation to magnesium, at the least a magnesium level should be checked with the initial set of electrolytes and hypomagnesemia should be treated. The dose for critical asthma and hypomagnesemia can be the same 25 to 45 mg/kg given over 30 minutes. Magnesium toxicity can include muscle weakness, cardiac arrhythmias, decreased reflexes, and respiratory depression.

**Helium.** Mixtures of helium and oxygen (heliox) can be used to improve laminar gas flow. This occurs due to the decreased density of helium as compared with nitrogen (approximately one-seventh). For Helium to be beneficial in small airways, it must occur in a high ration with oxygen. The greatest benefits may be seen with an 80:20 or 70:30 ratio of helium:oxygen. Therefore, hypoxemia and the need for increased supplemental oxygen may limit heliox use. There is data supporting the use of heliox as a method of delivering inhaled  $\beta_2$  agonists.<sup>446</sup> As with other advanced therapy, helium may not have a role in routine care, but there may be benefit from its use in severe critical asthma.

**Ketamine.** Ketamine is a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist that can produce a state of dissociative anesthesia. An additional effect of ketamine is bronchodilation. It is a useful medication for sedation in the ICU as ketamine has limited effect on the respiratory drive, and in usual doses, hemodynamics are not usually affected. For patients with asthma who are intubated and mechanically ventilated, ketamine may be a good choice for sedation along with a benzodiazepine. Further, there was one pediatric study<sup>447</sup> showing an improvement in the  $\text{PaO}_2/\text{FiO}_2$  ratio as well as dynamic compliance in mechanically ventilated children with refractory bronchospasm who were receiving a continuous infusion of Ketamine. There has been no study to show whether ketamine used to treat anxiety is beneficial in preventing intubation in patients during an asthma attack. For non-intubated patients, a recent Cochrane Database Review<sup>448</sup> did not show significant benefit in severe acute asthma. If a decision is made to use ketamine either for a procedure or a means of sedation, the bolus dose is usually 1 mg/kg, allowing time for effect before repeating. Ketamine is given as a continuous infusion at the dose of 5 to 30  $\mu\text{g}/\text{kg}/\text{min}$  titrated to effect. One of the additional side effects of ketamine can be dysphoria, and as such it is usually given with a benzodiazepine.

**Noninvasive Ventilation.** There is very limited evidence that NIV is effective in children with asthma.<sup>335</sup> Clinically patients with effective air exchange who fight the mask and positive pressure do not benefit from NIV. Nevertheless, some children with very limited air exchange and fatigue take to NIV easily and appear more comfortable. NIV may allow time for therapies to become effective (steroids) and may prevent intubation. This should not be used when the level of alertness or ability to protect the airway is diminished.

**Intubation.** By the time patients with asthma require intubation and mechanical, they are hypoxic, acidotic, fatigued, and have limited reserve. It is suggested that the most experienced person available perform the intubation. Appropriate venous access is required, and fluid boluses may be necessary. Ketamine and a benzodiazepine have been recommended by many. Ketamine may produce increased secretions, so atropine should be considered. Ketamine may produce dysphoria so the benzodiazepine is given for its amnestic effects. The management style in our ICU is to get the patient back to breathing spontaneously or initiating their own breathes as soon as possible

after intubation. In turn, Rocuronium can be considered as medium short-acting muscle relaxant. Succinylcholine can be used, but the other side effects of this medication, including elevation of potassium, should be considered. A cuffed ETT is recommended, as ventilator settings may require high peak pressures. Immediately after intubation, we typically hand ventilate the patient with a low rate. This is to prevent alveolar overdistension and reduce the risk of pneumothorax. There can be acute decompensation following intubation. Hypovolemia and increased intrathoracic pressures may be an issue. Following the DOPE acronym, one should also look for **Displacement** or **Obstruction** of the ETT and rule out **Pneumothorax** or **Equipment** failure.

**Mechanical Ventilation.** There can be controversy regarding the best means to mechanically ventilate patients with asthma. The argument against setting the ventilator in a pressure control mode is that changes in airway resistance that occur with asthma can result in delivery of an inadequate tidal volume. The argument against a the ventilator in a volume control mode is that due to flow patterns of the ventilator the same tidal volume can be delivered with a higher peak pressure as compared with a pressure control mode. As stated before, our management style is to get intubated asthmatics breathing spontaneously as soon as possible. This allows them to set their own breathing rate, and on pressure support and PEEP, they can set their own inspiratory to expiratory ratio. Pressure support has been recommended because it is patient-initiated, even if not patient-limited.<sup>449</sup> There may be initial elevations in  $\text{PaCO}_2$ , but if the patient is well oxygenated, the carbon dioxide elevation is usually well tolerated.

Historically, clinicians set zero or low PEEP for intubated asthmatics due to the perceived risk of hyperinflation<sup>450</sup> and barotrauma. However, since 1988 there have been four adult studies<sup>451-454</sup> and one pediatric study<sup>277</sup> strongly suggesting the benefits of extrinsic PEEP during mechanical ventilation for intubated asthmatics. These studies demonstrated that extrinsic PEEP, up to a level to matching intrinsic PEEP, improves the triggering sensitivity of the ventilator, diminishes ventilatory work, and reduces mechanical work of breathing for patients spontaneously breathing with assisted ventilation. As the work of breathing is reduced, there is improved patient comfort and potentially a reduced need for sedation. It is felt that matching extrinsic PEEP applied with the ventilator to the intrinsic PEEP developed by the patient with asthma may improve delivery of aerosol therapy via the ETT. Matching PEEP may possibly result in earlier liberation from mechanical ventilation. It should be noted that some clinicians believe that attempts to match PEEP may include the risk that extrinsic PEEP will cause overdistension of the lungs. Overdistension of the lungs may increase the risk of hyperinflation and air leak syndrome.<sup>450</sup> Our studies<sup>277,287</sup> indicate that spontaneous breathing with pressure support and PEEP lowers WOB. For the individual patient, the level of extrinsic PEEP at which hyperinflation will occur is unknown. Theoretically, for the spontaneously breathing patient, extrinsic PEEP applied to counteract intrinsic PEEP should not cause an increase in end-expiratory lung volume (EELV) until extrinsic PEEP exceeds intrinsic PEEP.<sup>455</sup> Further, the EELV may even decrease, leading to decreased dead space

and increased compliance. In our ICU intrinsic, PEEP is measured during a ventilator pause, allowing the patient to exhale completely and measuring the pressure before the next breath. We gradually add extrinsic PEEP with the ventilator and observe RR and clinical work of breathing. We always keep extrinsic PEEP at a level below intrinsic PEEP. We continue to reassess the level of extrinsic and intrinsic PEEP as the patient responds to therapy. Further research is needed to determine the best practice of mechanical ventilation for intubated asthmatics, but this is limited by the small number requiring intubation each year.

**Inhalational Anesthetics.** One of the properties of inhaled anesthetics is bronchodilation. In turn, inhaled anesthetics have been used as rescue therapy in children with critical asthma who are intubated. We have used isoflurane in our ICU for its reduction in bronchospasm with the added benefit of a decreased sedation requirement. However, inhaled anesthetics are difficult to use in an ICU setting. Modern ICU ventilators are not designed to accept a vaporizer. There is no circle system in ICU ventilators, so there is a tremendous use of anesthetic vapor. There is no primary means of gas scavenging in an ICU ventilator, so significant steps must be taken to contamination of the patient room. There is a case series of six patients reported by Wheeler et al.<sup>456</sup> Dr. J. Tobias has published several articles<sup>457-459</sup> detailing the use of inhaled anesthetics in asthma and other clinical conditions. A recent retrospective cohort study by Char et al.<sup>460</sup> in intubated asthmatics did not demonstrate a difference in mortality between centers that did or did not use inhaled anesthetics. There was significantly greater length of mechanical ventilation, greater length of stay, and increased hospital charges in the centers using inhaled anesthetics. The significant

expertise needed to safely deliver inhaled anesthetics may limit its use to a few centers. An anesthetic conserving device (AnaConDa Sedana Medical) is available in the European market but not the United States. The device is a miniature vaporizer and a conserving medium or reflective filter that keeps the inhaled anesthetic on the patient side of the device. This device can be used with a normal ventilator. Finally, as the scientific community learns more about the potential neurotoxicity with inhaled anesthetics, the physician must weigh the risk and benefit profile to long-term inhalational anesthetics for the management of status asthmaticus.

**Extra Corporeal Life Support for Status Asthmaticus.** ECLS has been used as a rescue therapy in near fatal asthma. As with inhaled anesthetics, the use of ECLS for this indication is likely limited to a small number of centers. One single center study reports<sup>35</sup> their use, but the number of patients (13 total) is too small to determine whether this therapy has advantages over mechanical ventilation or conventional therapy.

## Pulmonary Hypertension

### CENTRAL NERVOUS SYSTEM

Systemic illness is a common cause of CNS dysfunction in infants and children. Seizures, head trauma, CNS infections, and hypoxic or metabolic encephalopathy commonly cause acute neurologic dysfunction in the PICU. Assessment of neurologic function depends on an understanding of the age-dependent progression of motor and cognitive skills. Table 79.8 lists the developmental milestones.

**TABLE 79.8** Normal Ages for Major Developmental Milestones

Age	Motor Function	Language	Adaptive Behavior
4-6 weeks	Lifts head from prone position and turns from side to side	Cries	Smiles
4 months	Shows no head lag when pulled to sitting from supine position; tries to grasp large objects	Utters sounds of pleasure	Smiles, laughs aloud, and shows pleasure from familiar objects or persons
5 months	Grasps voluntarily with both hands; plays with toes	Makes primitive sounds	Smiles at self in mirror (ah, goo)
6 months	Grasps with one hand; rolls prone to supine; sits with support	His increased range of sounds	Expresses displeasure and food preferences
8 months	Sits without support; transfers objects from hand to hand; rolls supine to prone	Combines syllables (baba, dada, mama)	Responds to "No"
10 months	Sits well; crawls; stands holding; finger-thumb apposition in picking up small objects		Waves goodbye; plays patty-cake and peek-a-boo
12 months	Stands holding; walks with support	Says two or three words with meaning	Understands names of objects; shows interest in pictures
15 months	Walks alone	Utters several intelligible words	Requests by pointing; imitates
18 months	Walks up and down stairs holding; removes clothes	Says many intelligible words	Carries out simple commands
2 years	Walks up and down stairs by self; runs	Makes two- or three-word phrases	Engages in organized play; points to some parts of the body

## Functional Postnatal Neurologic Development

Motor function in the newborn depends on gestational rather than postnatal age. That is, an infant born at 28 weeks' gestation exhibits motor responses similar to those of a full-term newborn when the former is 3 months old. Although potentially modifiable by cortical influence, most neonatal motor behavior is subcortically controlled, which permits normal motor behavior in newborns who have severe cortical damage. Assessment of intellectual development is difficult in a newborn; initially, it is based on the absence of reflexes and the acquisition of new motor skills. Adaptive or interactive behavior is first seen with accommodation to repeated stimuli and eye contact. The infant's intellectual development depends on the presence of external stimulation and social interaction, preferably from one or a few individuals. This is why infants and children who require long-term intensive care must have parental input and developmental stimulus.

## Assessment of Neurologic Function

Clinical examination is the most important tool we have for assessing neurologic function in children. In an awake child, interactions with the examiner and caretakers are sensitive indicators of high or integrative cortical function. When the child's cognitive function is depressed from disease or drugs, examination of the general level of activity and peripheral and brainstem reflexes becomes an important, albeit crude, measure of CNS function. A detailed examination includes an evaluation of the level of consciousness and alertness in the context of sedative medications. The Glasgow Coma Scale (GCS) is a commonly accepted tool to evaluate the level of function of neurologically impaired

patients (Table 79.9); however, it was not developed for this purpose, and extensive research needs to continue on directed scales and noninvasive means to improve assessment consciousness in the critically ill child.<sup>461</sup> Painful stimulation can stimulate both decorticate or decerebrate posturing and likely indicates significant CNS malfunction and should trigger further investigation. Decerebrate posturing is an extension at the elbows with the arms and hands pronated, whereas decorticate posturing of the upper extremities is flexion at the elbows with the hands clenched. These responses to painful stimuli or no response at all should (in combination with attempts to elicit a cough, gag, or ability to handle oral secretions) make the practitioner question whether the patient can protect their airway. Pupillary reflex is a well preserved function, and therefore unreactive pupils are very concerning. Large reactive pupils may be caused by tricyclic antidepressant ingestion, atropine administration, or a symptom of pharmacologic withdrawal. Small reactive pupils may indicate damage at the level of the pons, but usually indicate the presence of opioids or barbiturates. Fundoscopic exam is important to assess for signs of increased ICP or retinal hemorrhage; however, the bedside practitioner may have difficulty with these assessments, and it may require an ophthalmologist consultation.

## Laboratory Assessment of Neurologic Function

The EEG is used to diagnose seizures and isoelectric brain death and to monitor the effects of barbiturates administered to induce coma. In addition, continuous EEG monitoring is often used to detect nonconvulsive seizure activity in critically ill children.<sup>226,462,463</sup> This is a resource-intense monitoring system that has yet to show that it improves

**TABLE 79.9** Glasgow Coma Scale for Infants and Children

Activity	Adult/Child Response	Infant Response	Score
Eye opening (E)	Spontaneous	Spontaneous	4
	To verbal stimuli	To verbal stimuli	3
	To pain	To pain	2
	None	None	1
Best verbal response (V)	Oriented, appropriate	Coos and babbles	5
	Confused conversation	Irritable cries	4
	Inappropriate words	Cries to pain	3
	Incomprehensible words	Moans to pain	2
	None	None	1
Best motor response (M)	Obey verbal command	Normal movement	6
	Localizes stimulus	Withdraws upon touch	5
	Withdraws from noxious stimulus	Withdraws upon pain	4
	Decorticate flexion	Decorticate flexion	3
	Decerebrate extension	Decerebrate extension	2
	None (flaccid)	None (flaccid)	1

outcomes; however, its use continues to grow in neonatal and pediatric critical care, and further study is needed for this promising noninvasive tool. CT allows rapid detection of CNS lesions, the extent of structural injury, and noninvasive assessment of ICP. Cranial ultrasound is a bedside technique used to assess ventricular size and intracranial anatomy in infants with nonfused cranial sutures. MRI permits intraorbital and ocular injuries and brainstem and spinal cord lesions to be examined; it is also good for defining soft tissue abnormalities.<sup>464</sup> MRI's major drawback is the length of time required for each examination and the relative inaccessibility of the patient while in the scanner. Maintaining body temperature can also be a problem in small children during MRI scanning because the room must be cold. It may be difficult to safely perform MRI in patients who have significant cardiorespiratory compromise because many of the pumps and ventilators cannot enter the scanner. Doppler ultrasound allows bedside assessment of CBF velocity in the ICU. Although it does not directly measure CBF, Doppler ultrasound is a useful bedside guide to therapy. CBF scans are the "gold standard" and are usually required to diagnose brain death during barbiturate coma. ICP can be monitored by inserting a catheter into a lateral ventricle or by inserting a subarachnoid screw or transducer into the epidural space or cerebral parenchyma. The ventricular catheter provides an accurate waveform and permits withdrawal of cerebrospinal fluid (CSF) to reduce ICP. The other devices used to measure ICP provide less consistent pressure waves and do not permit removal of CSF.

### Traumatic Brain Injury

Despite advances in resuscitation care, morbidity following pediatric TBI remains high. TBI is composed of two components, an initial primary injury due to direct mechanical deformation of brain parenchyma, and a subsequent secondary injury that may develop over hours to days. Secondary injury may be the result of multiple mechanisms including ischemia, excitotoxicity, metabolic failure and eventual apoptosis, cerebral swelling, axonal injury, and inflammation and regeneration.<sup>465</sup> For improvements in outcome to be achieved in the pediatric critical care setting, secondary brain injury must be prevented or minimized.

Conventional wisdom about TBI has dictated that ischemia plays a major role in secondary brain injury. While reversal of ischemia is crucial, simply delivering oxygen to injured areas of the brain does not abate the onslaught of secondary injury cascades destroying vulnerable areas of brain following TBI. Recent evidence suggests that secondary injury persists despite adequate oxygen delivery to brain tissue due to persistent metabolic crisis.<sup>466,467</sup> Furthermore, hyperoxia is not effective in completely reversing metabolic crisis and may lead to persistent secondary injury due to superoxide and free radical generation. There is widespread heterogeneity of metabolism following TBI, with some regional areas of increased glucose and oxygen utilization (likely due to electrical instability); however, in large regions of the brain, oxidative metabolism is reduced to a critical threshold with critically low rates of CMRO<sub>2</sub>.<sup>468</sup> This coupled with ongoing low CBF following TBI places viable brain tissue at risk.<sup>468,469</sup> How the neurovascular

bundle regulates the delivery of blood flow to regions gripped in metabolic crisis in ongoing secondary crisis and determining how to manipulate CBF remains an important avenue of study in the immature brain.

### Cerebral Perfusion Pressure and Cerebral Blood Flow

In children, developing effective treatments for TBI is complicated by the rapid changing responses of the immature brain to each type of brain injury during development from infancy through childhood.<sup>470,471</sup> Therefore, evaluation of therapies for children with brain injury must utilize immature animal models as a translational pathway to human trials in children. It must be understood that much of the research in this field that drives clinical guidelines and recommendations are born from adult clinical studies and adult aged small animal research. How this evidence translates to the child provides some direction but should catalyze further research focusing on the immature brain. This is especially true when the practitioner must indirectly target metabolic delivery in the face of secondary brain injury by attempting to modulate CBF and predict regulation or lack of regulation in the neurovascular bundle. Even in the healthy brain, CVR regulation is complex and poorly understood.<sup>472-474</sup> To add to this layer of complexity, CVR is likely heterogeneous following brain injury dependent on the mechanisms of injury, age, and even gender. Optimal global CBF is an elusive clinical target, with a lower inflection point associated with ischemic injury and an upper inflection point associated with hyperemia increasing cerebral blood volume and ICP. In early posttraumatic brain injury, cerebral hypoperfusion may greatly contribute to secondary brain injury, ultimately increasing morbidity and mortality.<sup>469,475</sup> In adults, areas of contusions have low CBF similar to the ischemic penumbral zones surrounding areas of acute ischemic stroke.<sup>476,477</sup> Low CBF states have been demonstrated in children by xenon CT scans following TBI within 24 hours of the initial injury, but by 48 hours these patients had normal or supernormal blood flows.<sup>475</sup> Furthermore, CBF in pediatric patients as a target for neuro-resuscitation is a theoretical point of manipulation due to limited options of continuous measurement in the clinical setting. Therefore, CPP (mean arterial blood pressure [MAP] minus ICP) is a commonly used surrogate.

When cerebral autoregulation is impaired, CBF and the metabolic needs of the injured brain may depend on maintaining adequate CPP. The difficulty comes in identifying the term adequate. Currently, pediatric CPP thresholds (40-60 mm Hg) have been extrapolated from adult experimental and clinical TBI and stroke studies.<sup>476,478</sup> However, recently it has been reported in adults that ischemia following TBI may occur at much higher levels of CBF compared with stroke.<sup>476</sup> Chambers et al, have published much needed age-specific pediatric thresholds for critical CPP, below which cerebral ischemia occurs with unfavorable neurologic outcomes and increased mortality.<sup>479-481</sup> These studies identified inadequate CPP levels but did not identify an "optimal treatment" CPP, and therefore assumed that these CPP levels were equivalent to brain injury insult thresholds.

It is not clear if a CPP of 40 mm Hg is a minimal threshold and/or that an optimal CPP to prevent brain injury may be higher.<sup>482</sup> Using currently accepted pediatric CPP guidelines (CPP >40 mm Hg) may not ensure adequate oxygen delivery to brain tissue.<sup>483,484</sup> This raises the question: is a CPP greater than 40 mm Hg in the pediatric TBI patient high enough? Mild induced hypertension after ischemic stroke has shown promise in animal models but remains controversial in the clinical setting.<sup>485,486</sup> Adult TBI studies have observed an increased risk of adult RDS associated with targeting a CPP greater than 70 mm Hg, but it is unclear how applicable this is to pediatric neurocritical care.<sup>487,488</sup> A retrospective study of 146 pediatric TBI patients observed a strong association of poor outcome at discharge with hypotension within the first 6 hours of injury.<sup>489</sup> The window for treatment of hypoperfusion appears to be early after pediatric TBI, and may be of relatively short duration in children. We believe that early aggressive intervention of blood pressure support especially during early critical periods, such as initial resuscitation of a multitrauma patient, intubation, placement of support lines and neuromonitoring devices is critical to neuro-resuscitation. Guidelines released in 2012, based on Class III evidence for pediatric traumatic brain injury, suggest that a minimum CPP of 40 mm Hg should be maintained and that 50 mm Hg for a minimum CPP in older children may be required.<sup>490</sup> However, data in our laboratory in large animal models of TBI may support the use of higher CPP support (>70 mm Hg) in severe TBI.<sup>491</sup>

Targeting CPP often requires vasopressor support. While central venous access should not delay administration of vasopressor support, it is important to understand the risks of extravasation of these infusions and have qualified individuals place central venous access as soon as possible to mitigate these risks. Initial stabilization of the pediatric TBI patient may occur in limited resource environments where complex invasive intracranial monitoring may not be available. Early stabilization of cerebrovascular hemodynamics with phenylephrine and targeting a higher MAP or CPP may reduce brain injury and improve long-term outcomes. A common first-line vasopressor to improve MAP in pediatric brain injury is phenylephrine. Phenylephrine is an  $\alpha$  adrenergic agonist that may have little or no effect on cerebral vasculature resistance.<sup>492-495</sup> Another vasoactive medication gaining favor is NE. NE primarily targets alpha-receptors for peripheral vasoconstriction, but has additional effects on  $\beta$ -receptors increasing inotropy. There are several published reports now in adults that show the rising use of NE as a preferred vasoactive medication and may provide more predictable CPP augmentation when compared with dopamine.<sup>496-498</sup> Prathee et al. have reported that adults with isolated traumatic brain injury and cardiac dysfunction have a higher incidence of in-hospital mortality.<sup>499</sup> Further research is critical to determine the degree of cardiovascular compromise following TBI in children and which vasopressor should be considered a first-line agent in pediatric brain injury; this currently should be determined by local experience and comfort of use. We believe that the next generation of treatments will build upon the tenets of ischemic neuro-resuscitation and combine early directed metabolic neuroresuscitation.<sup>500</sup>

## Respiratory Management in the Brain Injured Child

**Airway Management.** The comatose and brain-injured patient is at severe risk for respiratory failure due to loss of airway protective reflexes and impaired central regulation of respiratory function. In addition, progression of ALI and ARDS can be exacerbated by concomitant injuries (pulmonary contusions, aspiration, left ventricular dysfunction or failure, and inflammation due to systemic inflammation due to trauma or infection) and treatments to improve cerebral perfusion (crystalloid administration, hyperchloremic metabolic acidosis, hypernatremia, and vasopressor therapy). It is critical that the physician caring for these patients have a neuroprotective plan in place for induction and intubation, as well as adequate training and skill to obtain an artificial airway. In addition, the physician needs to be adept at ongoing neuro-resuscitation in the face of progressive lung disease and hemodynamic instability from SIRS and rising MAPs impeding cardiac preload. The initial step in treating the head-injured pediatric patient is always to promote adequate oxygenation and ventilation, and to prevent or treat hypotension thereby limiting ischemia. Criteria for tracheal intubation include hypoxemia not resolved with supplemental oxygen, apnea, hypercarbia ( $\text{PaCO}_2 > 45$  mm Hg), GCS  $\leq 8$ , an incremental decrease in GCS greater than 3 independent of the initial GCS (combined with clinical correlation, anisocoria greater than 1 mm, cervical spine injury compromising ventilation, loss of pharyngeal reflex, and any clinical evidence of a herniation pattern or Cushing triad).<sup>501</sup>

**Induction and Intubation.** Patients with neurologic injury are at a high risk for aspiration during induction of anesthesia, due to loss of airway protective reflexes. In addition, there is a heightened risk of cervical spine injury due to trauma and most patients will be in a cervical collar requiring manual in-line stabilization. The goal of intubation in the neurologically impaired patients should be (1) rapid sequence from induction to placement of an ETT to reduce the risk of pulmonary aspiration; (2) blunt nociceptive reflexes that may further elevate ICP or cerebral hypertension that may exacerbate intracranial hemorrhage or facilitate herniation; (3) maintaining adequate, age-appropriate CPP; and (4) limiting ischemia by maximizing adequate oxygen delivery and maintaining  $\text{PaCO}_2$  in a normal range to ensure appropriate CBF.<sup>502</sup> It should be assumed that all patients are at risk for a full stomach and cervical spine injury, so intubation should be performed utilizing a neuroprotective, rapid-sequence induction whenever possible. Supplemental oxygen (100%) should be delivered by face mask to allow nitrogen washout from the patient's FRC to allow sufficient oxygenation prior to tracheal intubation attempts. To avoid risk of aspiration bag-valve-mask (BVM) ventilation should not be done, unless the patient has signs and symptoms of impending herniation or life threatening desaturation events. Outside of impending herniation, if BVM ventilation is conducted it is imperative to not over-ventilate the patient, decreasing  $\text{PaCO}_2$  and thereby increasing cerebral vascular resistance, resulting in decreased CBF and metabolic delivery in a brain-injured patient. A separate health care professional's sole responsibility is to maintain the child's neck in a neutral position by

mild axial traction during airway maneuvers to prevent or perpetuate cervical spinal injury. Cricoid pressure should be done by a third individual only if the individual is appropriately trained in the technique and it should be abandoned if it hinders a rapid intubation attempt. Orotracheal intubation by direct laryngoscopy should be performed, and nasotracheal intubation should be avoided due to potential for direct intracranial damage in a patient with a basilar skull fracture.

Because tracheal intubation is a noxious stimulus and can increase ICP, appropriate sedative and analgesic medications should be administered during rapid-sequence induction. The hemodynamic and neurologic status of the patient dictates the choice of agents. Patients usually receive lidocaine (1-1.5 mg/kg) intravenously before intubation to help blunt the rise in ICP that occurs during direct laryngoscopy.<sup>73</sup> For the hemodynamically unstable patient, the combination of lidocaine, etomidate (0.2-0.6 mg/kg), and neuromuscular blockade with rocuronium (1 mg/kg) or succinylcholine (1 mg/kg) IV is a popular choice. The authors believe that succinylcholine may still be an option for rapid sequence intubation (RSI) in children who may be a difficult airway due to its rapid recovery, as opposed to the non-depolarizing intermediate neuromuscular blockade of rocuronium. There are several choices for induction agents in the critically ill child with acute brain injury. In the following sections, we will discuss the pros and cons of each induction agent. It still remains unclear if any of these agents have particular advantages or disadvantages for patients with brain injury, all have been implicated in animal studies as neuroprotectants and neurotoxins. But what is clear is that they are essential to the care of these patients and practitioners should stay current with literature and consider the pharmacodynamics of each drug.

**Etomidate.** Etomidate is a short-acting IV drug that produces sedation, anxiolysis, and amnesia. Side effects include respiratory depression, hypotension, myoclonus, and adrenal suppression; and it should not be used in children with suspected adrenal insufficiency and sepsis.<sup>503</sup> Etomidate has the benefits of decreasing ICP by reductions in CBF and CMRO<sub>2</sub> and has the advantage of producing less cardiovascular depression than barbiturates or propofol, preserving CPP.<sup>504,505</sup> These neuroprotective qualities are counterbalanced by its ability to increase cerebral vascular resistance by a greater magnitude than its reduction of CMRO<sub>2</sub> resulting in an increased metabolic deficit.<sup>506,507</sup> The increased metabolic deficit has the potential to expand the ischemic core and penumbra in brain injured tissue. This increase in cerebrovascular tone is thought to be attributed to etomidate's inhibition of NO synthase.<sup>508</sup> Particular attention should also be paid to the rapid recovery of etomidate, once the airway is secured etomidate's effects on consciousness dissipates quickly, principally due to the redistribution of the drug from the brain to inactive tissue sites. Recovery of consciousness can be between 5 and 15 minutes, and if rocuronium (paralyzed for approximately 45 minutes) is used in combination for RSI, the patient will need ongoing sedation while paralyzed. The addition of a short-acting opioid such as fentanyl may be necessary, especially if the

patient has concomitant injuries, such as bone fractures. An alternative is the combination of lidocaine, fentanyl (1-4 µg/kg), and rocuronium. In the hemodynamically stable patient, either of the provided combinations with fast-acting benzodiazepine midazolam (0.05-0.2 mg/kg) can be added. In addition, the short-acting narcotic fentanyl, when used with lidocaine, can decrease the catecholamine release associated with direct laryngoscopy.<sup>509</sup>

**Ketamine.** Ketamine is a phencyclidine derivative typically formulated as a mixture of two enantiomers in a hydrochloride salt form. It possess of low pH of around 4, which can produce pain at the injection site when administered intramuscularly or intravenously. Ketamine is a NMDA antagonist, which produces increases in CBF and CMRO<sub>2</sub>.<sup>510,511</sup> Early studies in patients with obstructed CSF pathways reported ketamine administration increase ICP with reductions in CPP.<sup>512,513</sup> More recent studies in adult patients with severe head injury have demonstrated improvements in CPP and minimal increases in ICP with ketamine.<sup>514-516</sup> One recent report of 30 intubated pediatric head injury patients observed that single doses of ketamine lowered ICP without producing decreases in blood pressure or CPP.<sup>517</sup> It is still unclear what ketamine's effect is on neurologic outcome in these patients or in patients where ventilation is not being tightly controlled. However, we believe that ketamine can be used in the brain injured patient, especially in multitrauma patients and if etomidate is not indicated.

**Propofol.** Propofol is a short-acting sedative-hypnotic IV agent that can be used to provide moderate or deep sedation. Propofol can induce a deep state of sedation rapidly, provide a short duration of effect, and have a pleasant recovery phase. Propofol is a very popular agent for sedating pediatric patients with neurologic conditions for non-invasive diagnostic imaging, such as a CT scan or MRI. Due to the fast onset and recovery following administration, repeated neurologic examinations are easy to assess such as a child with sickle cell disease who comes in with altered mental status due to a stroke. Propofol also has anticonvulsant properties and reduces ICP, which can be advantageous in sedating a patient with epilepsy or a patient with concerns for obstructive hydrocephalus due to a malfunctioning ventriculoperitoneal shunt to obtain diagnostic neuroradiologic imaging.<sup>518</sup> While there have been cases of propofol providing adequate sedation and successfully treating intracranial hypertension,<sup>518,519</sup> several pediatric traumatic brain injury case reports have reported metabolic acidosis and death in patients on prolonged (24 hours) continuous infusion of propofol.<sup>520-524</sup> Furthermore, a rare but potentially fatal "propofol infusion syndrome," associated with lactic acidosis, hyperlipidemia, and multiorgan system failure, was first described in pediatric patients who received prolonged (24 hours) continuous infusion and at higher dosages (>4.5 mg/kg/h).<sup>525</sup> Current guidelines suggest, that in the care of pediatric traumatic brain-injured patients, "continuous infusion of propofol is not recommended."<sup>526</sup> Adverse effects of propofol include pain at the injection site, apnea or respiratory depression, hypotension, and bradycardia,

which can be detrimental in a patient at risk for brain ischemia. If used particular attention should be paid to the decrease in mean arterial blood pressure with the administration of propofol. Crystalloid bolus and vasopressor usage will likely be needed to counteract the effects of propofol to maintain proper CPP and avoid ischemic insult. Propofol does not provide any analgesia.

**Dexmedetomidine.** Dexmedetomidine, a centrally acting  $\alpha_2$ -adrenergic agonist, is a recently FDA-approved agent used for short-term (<24 hours) continuous IV sedation of adults who are tracheally intubated.<sup>527</sup> Like propofol, it has a rapid onset and a relatively rapid elimination half-life and is administered as a loading dose followed by continuous IV infusion. One of the advantages is that it provides sedation with a lower risk of respiratory depression than many other sedative medications. There is increased interest with this agent as a sedative during non-invasive neuroradiologic imaging studies in children who are not intubated. In one study, dexmedetomidine was compared with propofol in children undergoing MRI studies.<sup>528</sup> While the onset of sedation and recovery time were significantly shorter in the children that received propofol, hypotension, respiratory depression and desaturation were more common compared with the children receiving dexmedetomidine.<sup>528</sup>

There is increased interest in the use of dexmedetomidine as a sedative and potential neuroprotective agent in both adults and children, as animal studies revealed neuroprotection from hypoxia-ischemia and decreased apoptosis, and adult human studies in healthy volunteers demonstrated parallel decrease in cerebral metabolic rate for oxygen and CBF, which may potentially be helpful in briefly sedating patients who are at risk for intracranial hypertension, such as head trauma, brain tumor, and obstructive hydrocephalus.<sup>529</sup> In pediatric traumatic brain injury case reports, no detrimental effects on their ICP were observed. However, systemic hypertension was observed in one child who was receiving dexmedetomidine with other sedatives, while bradycardia was observed in two other children who were receiving dexmedetomidine, other sedatives, and therapeutic hypothermia.<sup>530,531</sup> Further studies are warranted on the potential use of this agent in children at risk for intracranial hypertension. The most common adverse side effects of dexmedetomidine appear to be cardiovascular. Bradycardia with rare reports of sinus pause or cardiac arrest has been reported. Hypotension has been reported as well as hypertension, the latter thought to be due to peripheral  $\alpha_{2B}$  agonism with peripheral vasoconstriction. There are conflicting reports on the effects of ventilatory function, with some studies suggesting mild respiratory depression, while others show no effect. While ICP does not appear to increase, CPP and CBF have been shown to decrease. The effects on seizure threshold appear to be mixed.<sup>532</sup> The authors do not recommend dexmedetomidine as an induction agent; however, it may be a useful agent for patients with brain injury and ongoing sedation needs; however, further study in pediatric patients is needed.

After successful tracheal intubation, oxygen saturation of 100%, normocarbia (35-39 mm Hg confirmed by arterial

blood gas and trended with an end-tidal CO<sub>2</sub>), and a chest x-ray showing the tracheal tube in good position above the carina (right mainstem tracheal intubation is common in pediatrics) should be confirmed. Unless the patient has signs or symptoms of herniation, prophylactic hyperventilation (PaCO<sub>2</sub> < 35 mm Hg) should be avoided. Hyperventilation causes cerebral vasoconstriction, which decreases CBF and subsequent cerebral blood volume—this will lower ICP, but may lead to ischemia.<sup>533</sup> However, in the presence of signs and symptoms of herniation, such as the Cushing triad (irregular respirations, bradycardia, systemic hypertension), pupillary dysfunction, lateralizing extremity weakness, or extensor posturing, hyperventilation with 100% oxygen can be a life-saving maneuver. Hyperoxia is to be avoided, once a stable airway is obtained, and FiO<sub>2</sub> should be titrated to maintain SaO<sub>2</sub> greater than 90%. Elevating the head to 30 degrees (with C-spine precautions) increases venous drainage and lowers ICP.<sup>534,535</sup> Furthermore, the head should be midline to prevent obstruction of venous return from the brain. If these maneuvers don't relieve the signs and symptoms of herniation, additional sedative and analgesic agents can be administered as long as hypotension is avoided.

**Supraglottic Airway Devices.** While supraglottic airways are not considered a permanent airway in critically ill patients, competency in placement is critical for all individuals participating in resuscitation of a brain-injured child. Supraglottic airway devices, such as a LMA device, can be lifesaving, and in a situation where there is difficulty with direct laryngoscopy and inadequate BMV, an LMA should be placed to limit hypoxia and control ventilation until a physician with advanced airway skills can arrive to place an ETT.

**Postintubation Stabilization.** After successful intubation, inspired oxygen should be titrated to maintain oxygen saturation greater than 90 percent, normocarbia (35-39 mm Hg confirmed by arterial blood gas and trends followed with end tidal CO<sub>2</sub>, unless there is impending herniation when it is acceptable to use moderate hyperventilation to 30-35 mm Hg), and confirmation of ETT position with a portable chest radiograph.<sup>533</sup> The head of the bed should be elevated to 30 degrees, and the patient's head should remain midline to improve venous drainage and lower ICP.<sup>534</sup>

**Neurologic Monitoring.** Recent guidelines published by Kochanek et al. provide an update on treatment for infants, children, and adolescents with TBI.<sup>536</sup> ICP increases when the intracranial volume of one of the four compartments (CSF, blood, brain, and supporting tissues) within the cranial vault increases. An increase in one compartment can occur without raising ICP if an equal volume is displaced from another compartment. When displacement is no longer possible, ICP rises in proportion to the added volume. In older children and adults who have a rigid calvaria, the cranial cavity is a closed container and the contents are noncompressible. In patients with a GCS of 8, there is Grade III evidence to place and ICP monitor.<sup>536</sup> Treatment of ICP should be considered when pressure is greater than

20 mm Hg; however, absolute goals are unclear children, and intermittent increases in ICP greater than 20 mm Hg may be associated with autonomic instability. Chesnut et al. have recently reported in a randomized control trial comparing intracranial monitoring with a strategy of imaging and clinical examination in adults with severe TBI.<sup>537</sup> While aspects of the study and recent evidence in adult severe TBI calls into question the utility of treating an ICP goal of 20 mm Hg, these goals should likely be used as a component of multimodal monitoring (MMM). The most common monitor used in TBI as an adjuvant monitor for MMM is brain tissue oxygenation (Licox, Integra). There is limited evidence in children, but in our center brain tissue, oxygen monitoring is a standard in children with severe TBI.<sup>484,538</sup> If brain tissue oxygenation is used, maintain partial pressure of brain tissue oxygen greater than 10 to 15 mm Hg. It is unclear how multimodal neurologic monitoring, both invasive (brain tissue oxygenation, microdialysis, CBF, intracranial EEG) and noninvasive, should be considered for advanced neuroresuscitation, but studies including the one by Chesnut et al. prove that future research is critical to understand the mechanisms, timing, and monitoring of the brain to limit secondary injury.

#### **Adjuvant First and Second Tiered Therapies for Intracranial Hypertension and Secondary Injury.**

In the 2012 guidelines<sup>536</sup> the use of hypertonic saline for intracranial hypertension is now grade II evidence and should be considered to reduce ICP in pediatric TBI. Use of 3% saline to treat increased ICP is gaining in popularity<sup>539</sup> because the sodium does not cross the blood-brain barrier quickly and it has an osmolar gradient similar to that of mannitol. Three percent saline has additional theoretical beneficial effects, including enhancement of cardiac output, reduction of inflammation, restoration of normal cellular resting membrane potential and cell volume, and stimulation of the release of atrial natriuretic peptide. Recommended dosing is 6.5 to 10 mL/kg IV bolus, but the practitioner may consider starting with small boluses and titrate to pharmacodynamics response. Repeat doses can be given but it is recommended to keep serum osmolality less than 320 mOsm/L. Prophylactic hyperventilation less to a PaCO<sub>2</sub> less than 30 mm Hg should be avoided. Mannitol reduces ICP by decreasing blood viscosity and transiently increasing CBF and oxygen transport. The adenosine concentration decreases and CBF is maintained in areas that have intact autoregulation. CBF remains constant despite a decrease in cerebral blood volume and ICP. Mannitol also reduces ICP by withdrawing water from the brain parenchyma and excreting the water as urine.<sup>540</sup> It takes 20 to 30 minutes for this osmotic effect of the drug to develop. Intermittent boluses of 0.25 to 1 g/kg of mannitol are administered intravenously to control ICP. The drug eventually enters the CSF and can increase ICP. Barbituates should only be considered for refractory intracranial hypertension. There is no evidence to recommend tight glucose control in head injured patients, nor is there evidence suggesting the use of immune modulating diets at this time. There is grade II evidence to suggest that antiepileptic therapy should be initiated in patients

with severe traumatic brain injury; in our institution, we placed continuous EEG monitoring and start prophylactic levetiracetam. Elevating the head of the bed 30 degrees while keeping it in the midline position enhances cerebral venous outflow. Even slight movement of the head to a few degrees off midline may double the ICP.

#### **Hypothermia for Severe Traumatic Brain Injury.**

Hutchison et al. published a multicenter randomized control trial to investigate the use of hypothermia as a neuroprotective strategy in children.<sup>541</sup> This trial concluded that children with severe TBI, where therapeutic hypothermia (32.5°C for 24 hours) was initiated within 8 hours of injury, there was no improvement in neurologic outcome and the hypothermic group had an increase in mortality. Subsequent analysis of this study suggests that the hypothermia group had a significant increase in hypotension and decreased CPP that may have contributed to the increase in mortality.<sup>542</sup> A second phase 3 randomized control trial was initiated to compare hypothermia and normothermia after severe TBI in children with a prolonged hypothermia window, 48 to 72 hours, and slower rewarming phase.<sup>543</sup> The study was terminated early for futility after interim analysis. Therefore, we believe current standard of care is normothermia for traumatic brain injury in children.

**Decompressive Craniectomy.** Decompressive craniectomy with duraplasty may be considered for pediatric patients with TBI who display early signs of deterioration, herniation, or refractory hypertension. Currently, there is an ongoing study in adults to investigate surgical decompression for severe TBI.

**Environment.** Care of patients with TBI within an organized trauma system has shown to reduce mortality associated with severe injury.<sup>544</sup> Unfortunately, most severe traumatic brain injuries occur in regions lacking in pre-hospital and advanced care in an ICU.<sup>545</sup> Critically injured children with traumatic brain injury should be stabilized and transferred to a level 1 trauma center as soon as possible.

#### **Hypoxic-Ischemic Encephalopathy**

There is little evidence that increased ICP or correction of ICP alters the outcome of patients with HIE. The clinical impression is that the outcome is less favorable in patients who have trauma or metabolic encephalopathy and that aggressive management of ICP, at best, prevents further CNS damage, which is important.<sup>546</sup> The GCS score provides a reasonable assessment of neurologic function in these patients.

#### **Hydrocephalus**

Another cause of increased ICP is an increase in CSF volume (i.e., hydrocephalus). Common causes of hydrocephalus include obstructed ventricular shunts, aqueductal stenosis/compression as a result of congenital malformations, infection, posterior fossa tumors, or intracranial bleeding. Inserting an external or internal shunt to reduce the volume of CSF can be lifesaving.

## Tumors

Brain tumors are common in children, and approximately 70% occur in the posterior fossa. The most common tumor type is astrocytoma. The initial symptoms may include focal deficits, ataxia, or symptoms of increased ICP. A change in condition following tumor resection requires an immediate neurologic evaluation and possibly a brain CT scan. Following a posterior fossa craniectomy, hemorrhage into the posterior fossa can compromise respiration, and if there is an externalized ventricular drain present, output should be carefully inspected. Postoperatively, the patient should be followed closely for syndrome of inappropriate antidiuretic hormone secretion (SIADH), DI, and cerebral salt wasting. SIADH usually occurs within 24 to 48 hours following surgery and results in the retention of free water and a decrease in serum electrolytes, which may rapidly worsen cerebral edema. Central DI usually follows the removal of a suprasellar tumor and results in significant diuresis when antidiuretic stores are exhausted with a resulting increased serum osmolality and a low urine osmolality and urine specific gravity (<1.005). DI is part of a typical triphasic (SIADH to DI to SIADH) response following suprasellar surgery and is treated with volume replacement, and a vasopressin infusion may be required.

## Status Epilepticus in Children

Status epilepticus is a continuous motor seizure that lasts for more than 20 minutes or a series of seizures without intercurrent awakening. Although it is common for physicians to never find a cause of the seizures, the most commonly diagnosed causes are infections (meningitis or encephalitis) and metabolic abnormalities (toxins, head trauma, and hypoxic and ischemic injury). Because seizure activity increases with status epilepticus, brain and skeletal muscle metabolism and oxygen consumption increase and place the child at risk for cellular hypoxia. During a seizure, airway obstruction and ineffective chest wall and diaphragmatic excursion can limit ventilation and worsen arterial hypoxemia and hypercapnia. Treatment of a seizure begins with establishing a patent airway, administering oxygen, and ensuring adequate ventilation. IV anticonvulsant drugs are given to stop the seizure. Commonly used anticonvulsants include lorazepam, phenobarbital, paraldehyde, and phenytoin. Lorazepam is a rapid and reliable drug used to stop seizures. Boluses of 0.1 mg/kg are given intravenously or rectally when there is no IV access. Phenobarbital, 5- to 10- mg/kg boluses (maximal dose of 20 mg/kg), also stops seizures. The main complication of lorazepam is respiratory depression when administered in high doses. Giving both phenobarbital and lorazepam together exaggerates the respiratory depression. Fosphenytoin is also given intravenously in doses of up to 20 mg/kg and should be administered slowly to avoid cardiovascular depression. Paraldehyde, 0.3 mL/kg, can be given rectally. Finally, an IV injection of 1 to 4 mg/kg of sodium thiopental stops most intractable seizures; higher doses of the drug may cause apnea, and the risk of vomiting and aspiration of gastric contents is real. Once the seizures are under control, the cause of the seizures must be determined.

## Renal System

**Functional Development of the Renal System.** Embryologic development of the renal system begins in the middle of the third week of gestation with development of the pronephric tubules. By 10 weeks' gestation, a functioning kidney and collection system exist, and fetal urine is discharged into the bladder. At 32 to 36 weeks' gestation, each kidney has a full complement of nephrons. Because the placenta is the major excretory organ of the fetus, renal growth is not governed by functional requirements. Renal growth increases linearly with body weight and body surface area during the third trimester of pregnancy. The glomerular filtration rate (GFR) increases rapidly from 28 to 35 weeks of gestation. At term, the GFR is 10 mL/min/m<sup>2</sup> and increases to 20 mL/min/m<sup>2</sup> by 2 weeks of age. Although the GFR of premature infants is lower, the rate of increase is the same as that in a term infant.<sup>547</sup> Tubular function is not fully mature in full-term newborns. The newborn kidney is sensitive to antidiuretic hormone (ADH) and vasopressin, and urine osmolarity can vary from only 50 up to 780 mOsm/L.<sup>548</sup> The tubular function of premature infants is less mature.

The newborn's renal threshold for bicarbonate is about 20 mEq/L, which means that standard acid-base nomograms do not apply to infants because their serum bicarbonate concentration of 20 mEq/L is not indicative of metabolic acidosis. The renal tubular glucose threshold of term infants is similar to that of adults, but it is only 125 to 150 mg/dL in premature infants. A full-term infant has 1% or less fractional excretion of sodium by the third day of life. Fractional excretion of sodium can be much higher (5%) in premature infants. Renin, angiotensin, and aldosterone concentrations are high in newborns and decrease over the first few weeks of life.

**Assessment of Renal Function.** In the resting state, the kidney receives 20% to 25% of the cardiac output, and due to autoregulation, the kidney maintains near constant renal blood flow and GFR. Creatinine is an end product of skeletal muscle catabolism and is excreted solely by the kidneys and blood urea nitrogen is a byproduct of protein metabolism. Values for BUN can increase independent of renal function as a result of dehydration, high protein intake, and degradation of blood from the GI tract. Normal values for pediatric renal function are presented in Table 79.10.

**Renal Pharmacology.** An important aspect of critical care is the maintenance of appropriate fluid balance in the critically ill child. Even in patients who have normal renal function, such as patients with ARDS, chronic lung disease, and CHF, diuretics are often used to limit lung edema and help with cardiorespiratory dysfunction. The ascending loop diuretic furosemide is likely one of the most widely used drugs in pediatric intensive care. Furosemide reaches the ascending loop of Henle by the way of the tubular fluid. A prescribed starting dose of furosemide is typically 0.5 to 1 mg/kg up to approximately 10 mg total dose for patients who are naïve to diuretic therapy. The lowest dose necessary to increase urine output should be used, to limit

**TABLE 79.10** Normal Values for Pediatric Renal Function

	Age	Value
Creatinine (mg/dL)	1 year	0.41 ± 0.1
	10 years	0.61 ± 0.22
	18 years	0.91 ± 0.17
Glomerular filtration rate (mL/min/1.72 m <sup>2</sup> )	2-8 days	39 (range, 17-60)
	6-12 months	103 (range, 49-157)
	2-12 years	127 (range, 89-165)
Urine concentration (mOsm/L)	1 month	600-1100
	2-16 years	1089 (range, 870-1309)

Modified from Goldsmith DL. Clinical and laboratory evaluation of renal function. In: Edelman CM Jr, ed. *Pediatric Kidney Disease*. Boston: Little, Brown; 1978:213.

toxicity including electrolyte imbalance and ototoxicity.<sup>549</sup> With progressive renal dysfunction, escalating doses of furosemide may be required to maintain the same clinical response. Electrolyte and renal function need to be monitored frequently, as diuretic therapy frequently causes significant hypokalemia and hypochloremia, as well as other electrolyte wasting. Furosemide is albumin-bound and, in low albumin states, often found in critical illness, the delivery of furosemide to renal secretory sites is decreased. Improved delivery and diuresis is often improved with the administration of 25% albumin just before or with the diuretic. The typical dose is 0.5 to 1 g albumin/kg. Additional diuretics acting at other locations such as hydrochlorothiazide (distal tubule) can be often used as adjuvant medications to improve diuresis. The drug spironolactone, which blocks the hormone aldosterone, is a weak diuretic but may prevent spare potassium loss. Failure of increasing amounts of diuretics to be effective likely represents worsening renal perfusion and/or renal failure.

**Renal Failure.** Acute renal failure is defined as an abrupt, often temporary loss of renal function (see Chapters 17 and 42), where there is insufficient removal of nitrogenous wastes and problems with fluid and electrolyte balance. Acute renal failure is described by (1) the area of obstruction (prerenal, postrenal [obstructive], or intrinsic renal disorders); and (2) the urine volume (oliguria, polyuria, and anuria). Urine composition is often altered, and fluid, electrolyte, and acid-base disorders are common in acute renal failure. Common causes include hypoperfusion, obstruction, toxins, drugs, inflammation, and autoimmune disorders.

Prerenal causes are common in the critically ill child due to systemic hypoperfusion and reduced renal blood flow, resulting in reduced urine output and results in azotemia and ischemic renal damage. *Azotemia* is the term for the accumulation of nitrogenous byproducts of protein metabolism. Intravascular fluids in the case of dehydration or fluids and inotropic support may be needed to reverse prerenal renal failure. The adequacy of circulating blood volume is assessed by CVP and cardiac output measurements, and by estimating renal blood flow with Doppler flow studies or nuclear imaging techniques.

Intrinsic renal failure is caused by disorders of the renal glomeruli, tubules, or blood vessels. Glomerular diseases include hemolytic-uremic syndrome (HUS), poststreptococcal glomerulonephritis, Henoch-Schönlein purpura, and other inflammatory and immune complex diseases. Acute tubular injury is most commonly caused by hypoxia and ischemia; other causes are rhabdomyolysis, sepsis, hyperthermia, hemolysis, and a myriad of nephrotoxins, including mercury, carbon tetrachloride, and ethylene glycol.

Postrenal obstruction of urine flow can occur anywhere within the collecting system, but it occurs most commonly as partial obstruction of the bladder neck or the ureterovesical or ureteropelvic junction. All these malformations cause obstructive nephropathy and renal injury or renal failure. Signs of obstruction may be subtle and require radiologic, ultrasonic, or endoscopic evaluation to detect. Recurrent urinary tract infections are frequent clinical manifestations of obstructive lesions.<sup>550</sup>

Vascular diseases, including arterial embolism, venous thrombosis, and congenital malformations, are also causes of acute renal failure.

**Hyperkalemia and Abnormalities of Sodium.** With increasing renal dysfunction there is a continued decrease in excretion of potassium. Hyperkalemia can lead to life-threatening cardiac arrhythmias and requires immediate treatment. ECG presentation of results in a peak in the T wave at moderately elevated potassium levels. As hyperkalemia increases, there may be ST segment depression, and widening of the QRS complex, leading to conduction abnormalities, bradycardia, ventricular fibrillations or asystole. Treatment includes removal of exogenous potassium (administration should be discontinued immediately) and calcium in the form of IV CaCl 10 to 20 mg/kg or CaGluconate 30 to 60 mg/kg to stabilize the cardiac cell membrane. IV sodium bicarbonate 1 to 2 mEq/kg will drive potassium into the intracellular fluid by increasing blood pH. Glucose and insulin also drive K<sup>+</sup> into cells. Glucose is given as 1 to 2 g/kg IV with insulin 1 unit per 4 g of glucose IV. If the patient is intubated, increasing RR makes blood more basic driving K<sup>+</sup> into the cells. It is important to note that none of these efforts will remove potassium from the body. Prior to the initiation of dialysis, potassium removal may be attempted with the ion exchange resin Kayexalate, a sodium polystyrene sulfate, which can bind potassium. It is given orally or rectally in suspension but does require excretion from the body. The dose is 1 g/kg orally, and it can be given every 6 hours; rectally, it can be given every 2 to 6 hours. The enema route is less effective than oral administration.

Severe hyponatremia and hypernatremia can be another electrolyte disturbance seen in the critically ill child. Hyponatremia may present with seizure activity, often when serum sodium is less than 120 mEq/L. In the presence of hyponatremic seizures, the initial treatment is the administration of 3% hypertonic saline with a goal to terminate seizure activity and raise serum sodium to greater than 124 mEq/L. However, in the absence of seizures, if a patient reached this low value slowly, it has to be corrected slowly, to potentially avoid osmotic demyelination. The same condition applies to hypernatremia. Rapid correction of elevated serum sodium is likely more harmful than the value itself.

#### BOX 79.4 Indications for Dialysis

1. Severe hyperkalemia
2. Metabolic acidosis unresponsive to therapy
3. Fluid overload with or without severe hypertension
4. Fluid overload with or without congestive heart failure
5. Uremia causing encephalopathy, pericarditis, or bleeding
6. Nonobstructive anuria
7. Inborn errors of metabolism
8. Certain drug overdoses
9. Significantly elevated ( $>100$ ) blood urea nitrogen possibly a relative indication
10. Potential treatment can reduce inflammation with sepsis or systemic inflammatory response syndrome

**Renal Replacement Therapy.** Renal replacement therapy may be required to improve ongoing fluid shifts and significant electrolyte disturbance (Box 79.4). Modalities for renal replacement therapy are commonly: peritoneal dialysis, hemodialysis, or continuous venovenous dialysis. Modality often depends on the size of the patient and the experience and resources of the institution.

Peritoneal dialysis (PD) has the benefits of being relatively low-cost, causing less hemodynamic compromise compared with venovenous filtration, requires no central venous line, and is technically simpler. This technique is especially effective in infants and smaller children. Peritoneal dialysis requires the insertion of a soft, multiholed catheter into the peritoneal cavity. When patency of the catheter is confirmed, a dialysate solution is infused that equilibrates with plasma and extracellular fluids. The parietal and visceral surfaces function as semipermeable dialysis membranes. The composition of the dialysis fluid is similar to that of plasma and consists of approximately 130 mEq/L of sodium, 100 mEq/L of chloride, 35 mEq/L of acetate or lactate as a buffer, 3.5 mEq/L of calcium, and 1.5 mEq/L of magnesium. The glucose concentration of the solution can be either isosmotic or hyperosmotic. Hyperosmotic solutions remove fluid and electrolytes. Respiratory compromise may occur with peritoneal dialysis because the increased abdominal pressure caused by the dialysate in the abdomen may prevent effective spontaneous ventilation. Mechanical ventilation will be required if this occurs. Bacterial or fungal peritonitis is common. Severe dehydration, circulatory collapse, and metabolic derangements are other complications of peritoneal dialysis.

The principles of hemodialysis are essentially the same as those of peritoneal dialysis, except the blood interfaces with a semipermeable membrane rather than with the peritoneum. Hemodialysis is more appropriate in the acute setting with life-threatening electrolyte disturbances, fluid overload, and toxic ingestions. Hemodialysis is more efficient than peritoneal dialysis. Hemofiltration and ultrafiltration are processes of convective solute transport. An ultrafiltrate of plasma is created by hydrostatic pressure exerted across a highly permeable membrane, with simultaneous blood volume replacement with a modified lactated Ringer solution.<sup>551</sup> Continuous venovenous hemofiltration (CVVHF) is a common form CRRT, which

provides isotonic fluid removal but minimal solute clearance. However, these circuits can be easily converted to perform dialysis, termed *continuous venovenous hemodialysis* (CVVHD), providing more solute clearance. In smaller patients, accurate flow rates are important in circumstances where more than 15% of the patient's circulating blood volume can be in the CVVHD tubing. Furthermore, technical challenges occur in smaller patients due to flow characteristics of smaller dialysis catheters. Hemodialysis can be performed with two separate 5 Fr single lumen catheters, but typically a dual-lumen 7 Fr catheter at a minimum is required. Anticoagulation for CVVHD can be either with heparin or with regional citrate administration. Citrate can be given in a stopcock prior to the machine, which creates a regional area of hypocalcium in the circuit, leading to relative anticoagulation in the circuit, while IV calcium is given back to the patient via a central line. The use of regional anticoagulation with citrate avoids the concerns of systemic anticoagulation and may reduce the risk of systemic bleeding.

**Renal Failure Outcomes.** The prognosis with acute renal failure depends on the patient's age, underlying disease, and the extent of the precipitating insult (also see Chapter 17 and 42). In general, children do better than adults; in fact, children usually recover completely from a renal insult if the hypoxia or ischemia lasted only a short time and other organ systems are not involved. Children with chronic renal failure require long-term outpatient peritoneal dialysis or hemodialysis until they can undergo renal transplantation.<sup>552</sup> It has been demonstrated that the degree of fluid overload at initiation of CRRT is associated with patient mortality.<sup>132</sup> This has been found to be independent of patient severity of illness scoring.

**Hemolytic-Uremic Syndrome.** HUS is one of the most common causes of acute renal failure in children. This syndrome is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute renal injury. In North America, HUS is most often associated with infection by cytotoxin-producing *Escherichia coli* O157, but other serotypes and other Shiga-like toxin-producing bacteria have been implicated.<sup>553</sup> *E. coli* O157 resides in the intestinal tract of cattle and may contaminate beef during processing.<sup>554</sup> The organism is killed by cooking. Infections can be spread by person-to-person contact in daycare centers, institutions, and the military. There is also a familial form of the disease that accounts for a small percentage of the total cases. HUS is seen predominately in 0.5- to 4-year-old children, but it can occur in all age groups.<sup>190</sup> It shares many laboratory and clinical features with the adult disease, thrombotic thrombocytopenic purpura. In fact, some investigators consider the two disorders a continuum of the same disease. The abnormalities that develop in HUS are believed to be caused by cytotoxins and lipopolysaccharide, a bacterial endotoxin. Toxin-induced damage to renal endothelial cells, the vasculature, and other organs is directly or indirectly associated with the activation of leukocytes.<sup>555</sup> Cytokines such as interleukin-1 and tumor necrosis factor, prostaglandin I<sub>2</sub>, thromboxane A<sub>2</sub>, and von Willebrand factor multimers probably play a role in the pathogenesis of this disease.<sup>556</sup> The time from exposure to

the organism to initial evaluation of the patient varies from 3 to 12 days. Symptoms last for about a week. Patients usually have abdominal cramping, bloody diarrhea, tenesmus, and vomiting.<sup>557</sup> On average, about 10% of children with *E. coli* O157-induced bloody diarrhea progress to HUS. Mildly affected patients exhibit anemia, thrombocytopenia, azotemia, and decreased urine output, and have an uncomplicated course. In severely affected patients, anuria is common, hypertension and seizures may occur, and the duration of illness is prolonged. A small number of children exhibit progressive and permanent renal insufficiency, severe and recurrent hemolysis, thrombocytopenia, and neurologic impairment. Hematologic abnormalities include hemolysis and thrombocytopenia. Hemolysis often causes hyperbilirubinemia and, despite reticulocytosis, severe anemia with hemoglobin concentrations of 4 to 5 g/dL. Thrombocytopenia is the result of platelet destruction and sequestration in the liver and spleen.<sup>558</sup> The remaining platelets show evidence of impaired aggregation.<sup>559</sup> Disseminated intravascular coagulation (DIC) is relatively common. Glomerular capillary endothelial injury is the most consistent renal finding in HUS. Acute renal failure with oliguria or anuria usually lasts less than a week but may linger for more than 10 weeks.<sup>560</sup> Glomerular or arterial injury, or both, may predominate, depending on the presence and extent of renal insufficiency (glomerular injury) and hemolysis and hypertension (arterial injury). CNS abnormalities are manifested as decreased levels of consciousness, seizures, irritability, ataxia, hypotonia, hemiparesis, hyperreflexia, and hallucinations; these problems may be caused by severe hypertension, electrolyte disturbances, microthrombi, or cerebral edema and increased ICP.<sup>561</sup> Abdominal cramping is common and may be difficult to distinguish from intussusception, intestinal stricture or bowel perforation, colonic gangrene, or other surgical emergencies.<sup>562</sup> Pancreatitis is common in patients with HUS. CHF may occur if there is fluid overload, hypertension, anemia, or myocardial depression caused by circulating endotoxins. Treatment of HUS is primarily supportive. Meticulous attention should be paid to volume status, electrolyte and acid-base balance, nutrition, antisepsis, and treatment of hypertension and coagulopathies. Enteric isolation is mandatory to prevent secondary spread of the disease. Accurate fluid intake and output measurements and frequent assessment of weight and volume status are important for management of these patients. A central venous catheter is useful for CVP measurements, blood sampling, and administration of IV medications and nutrition. Nephrotoxic drugs should be avoided if possible. If nephrotoxic drugs must be given, the drug dose should be adjusted and serum concentrations monitored closely. Daily fluids should be restricted to the amounts required to replace insensible losses, urine output, and other ongoing losses. Fluids administered should reflect the electrolyte content of the fluid losses. Caloric support is essential. Enteral feedings are preferred, but parenteral feeding may be necessary if ileus develops. Antidiarrheal medications prolong the duration of colitis, and antibiotics may increase the risk for HUS.<sup>563,564</sup> No specific treatment has been effective to date. Heparin, fibrinolytic agents, aspirin, dipyridamole, corticosteroids, vitamin E, and furosemide have not affected the outcome of HUS.<sup>201</sup> Immunoglobulin therapy,

plasmapheresis, and infusions of fresh frozen plasma have had mixed results, but no long-term therapeutic benefit has been demonstrated. Dialysis, improved nutrition, and supportive care have decreased the mortality rate from 100% in the original report to less than 10% in the last 30 years. Mortality rates remain high in developing countries and in children with a genetic predisposition for HUS.

## ENDOCRINE SYSTEM

### Adrenal Axis

Abnormalities of the adrenal axis result in deficient or excessive production of glucocorticoids, mineralocorticoids, or both. Many of these disorders are diagnosed and treated as they are in adults. Congenital adrenal hyperplasia, pheochromocytoma, and iatrogenic chronic adrenal insufficiency will be discussed briefly.

### Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia is an autosomal recessive disorder that is associated with deficiencies in either 21-, 11-, or 17-hydroxylase. 21-Hydroxylase deficiency in children can be partial (simple virilizing form) or more complete (salt-losing form); at birth, affected children demonstrate masculinization of the external genitalia, and those with the more complete deficiency show a progressive salt-losing state (i.e., loss of sodium and elevation of potassium). This condition is usually manifested in the first few weeks of life as feeding difficulty, vomiting, and failure to thrive. The clinical and historical course is suggestive of pyloric stenosis. If the deficiency is not diagnosed and treated early in life, affected children may suffer severe cardiovascular collapse. A blood sample should be obtained for electrolytes, glucose, and if the diagnosis has not been established, adrenocorticotrophic hormone (ACTH), cortisol, aldosterone, and plasma renin activity.

Treatment requires aggressive support of intravascular volume and myocardial function, glucose, and replacement of the deficient hormones. Cortisol can be replaced by oral administration of hydrocortisone at a dose of 25 mg/m<sup>2</sup>/day divided into three doses; if the child cannot tolerate oral medication, cortisone acetate can be administered intramuscularly at a dose of 37.5 mg/m<sup>2</sup>/day once every 3 days. For emergency therapy, when the oral route is not possible and perfusion of the muscle is poor, hydrocortisone acetate is used intravenously at a bolus dose of 1.5 to 2.0 mg/kg and then 25 to 250 mg/day in divided doses. Mineralocorticoid is replaced with cortisone acetate, 0.05 to 0.2 mg/day orally; these patients usually require the addition of salt to their diet. Deficiencies of 11- and 17-hydroxylase do not result in salt wasting; masculinization and hypertension are the common initial signs.

### Pheochromocytoma

Less than 5% of pheochromocytomas are diagnosed in childhood. As a rule, these tumors are confined to the adrenal medulla, but they can occur anywhere throughout the sympathetic chain. The clinical signs and symptoms of excessive catecholamines are the same as those in adults. Pre-, intra-, and postoperative therapy is similar to adults.

## Iatrogenic Chronic Adrenal Insufficiency

Long-term daily use of steroids for the treatment of asthma, nephrotic syndrome, and malignancies is common. Such use may cause a hypoadrenal state and increase the risk for cardiovascular collapse during a severe illness or stress. In children, topical steroids can also depress the production of ACTH. Replacement of stress-level steroids (three times the daily replacement dose) is required.

## Anterior Pituitary

Panhypopituitarism is usually secondary to a tumor or to aggressive dissection of a tumor.<sup>565</sup> Acute ICU problems related to this lesion include support of the adrenal axis and abnormalities of ADH.

## Diabetes Insipidus

DI can be of central, renal, or psychogenic origin. The central mechanism is the most common form in ICU patients. Absence of ADH results in polyuria and polydipsia; patients with a severe form of this disease may not be able to drink sufficiently to meet their requirement, and severe hypovolemia may develop. DI is precipitated by brain tumors, head trauma, neurosurgery, and clinical brain death.<sup>566,567</sup> Treatment, in the setting of the ICU, is fluid replacement or, if unwieldy, hormone replacement with aqueous vasopressin (Pitressin), 0.1 to 1.0 mL intramuscularly (duration, 4–6 hours); Pitressin tannate in oil, 0.25 to 1.0 mL intramuscularly (duration, 24–72 hours); or desmopressin acetate intranasal, 2.5 to 10 µg twice daily (duration, 10–11 hours). The clinical syndrome may be transient or chronic. In either case, close supervision of fluid intake and output is essential.

## Syndrome of Inappropriate Secretion of Antidiuretic Hormone

The syndrome of inappropriate ADH secretion is associated with hyponatremia and hypo-osmolality caused by inappropriate urinary loss of sodium and free water in patients with normal kidneys. Urine osmolality is greater than serum osmolality. This syndrome is precipitated by a number of mechanisms, including head trauma, neurosurgery, meningitis, hypoxia, and any major surgical procedure in which there is large-volume fluid shifts and fluid replacement.<sup>209,568</sup> This disease is usually self-limited, and the only real problem occurs if the diagnosis is not considered and the level of hyponatremia is low enough to cause CNS dysfunction. Seizures are rare unless serum sodium is less than 120 mEq/dL. Care should be taken to raise the serum concentration of sodium slowly. This syndrome is treated by fluid restriction and, in severe cases, by the infusion of hypertonic or isotonic saline.

## Pancreas/Insulin

**Hypoglycemia.** Hypoglycemia is a common problem in ICU patients. What constitutes hypoglycemia in children has been disputed. However, it is uncommon to find a blood glucose level below 40 mg/dL in normal, nourished premature, or term neonates. The usual symptoms of hypoglycemia include tachycardia, diaphoresis, weakness, mental clouding, seizures, and coma. The causes of hypoglycemia can be subdivided into disorders of

increased utilization and disorders of decreased production. Transient hypoglycemia of the newborn is caused by decreased or immature hepatic gluconeogenesis and it self-corrects within hours to days. If the hypoglycemia persists, hepatic enzyme deficiencies, endocrine problems, or hyperinsulinism (i.e., pancreatic cell abnormalities, infants of diabetic mothers) must be considered. Other causes of hypoglycemia in the neonatal period include sepsis, hypothermia, hypoxia, and transplacental exposure to maternal hypoglycemic drugs. In older children, hypoglycemia is associated with ketotic hypoglycemia,<sup>569</sup> hepatic enzyme abnormalities, hyperinsulinism, hepatic failure, and Reye syndrome, and it is a side effect of certain drugs. Regardless of cause, the initial treatment of hypoglycemia is glucose administration. The initial dose is 0.5 g/kg given as 50% dextrose in water (D<sub>50</sub>W). This dose should be followed by an infusion of dextrose that is sufficient to meet the metabolic requirements of the child (see the later section on the GI system).

**Hyperglycemia.** Hyperglycemia in the pediatric ICU can be separated into two main categories with distinct concerns and outcomes. Patients with Type I diabetes mellitus are often admitted to the ICU, with either initial presentation of the disease or those patients with known diabetes who are exhibiting recurrent problems of insulin balance. The second category of patients with hyperglycemia in critically ill children are those who develop elevated glucose during treatment for their underlying disease process, likely due to stress biology.

**Diabetic Ketoacidosis.** The most serious acute complication of diabetes mellitus is DKA, a syndrome of glucose and ketone overproduction and underutilization that causes hyperglycemic ketoacidosis. The clinical syndrome includes dehydration and hypovolemic shock from hyperglycemic osmotic diuresis, compensatory hyperventilation (Kussmaul pattern), life-threatening electrolyte depletion, and in cases of severe metabolic imbalance, neurologic obtundation and coma.<sup>570</sup> Laboratory evaluation demonstrates elevated blood glucose concentrations, severe metabolic acidosis, and compensatory hypocapnia, increased osmolality, hyperlipidemia, and a normal or low sodium level (usually fictitiously low because of the hyperlipidemia). Total-body depletion of potassium and possibly phosphate occurs. Levels of both may be falsely normal because of the metabolic acidosis.

Treatment of DKA requires careful correction of the metabolic derangements with meticulous monitoring of the multisystem complications of DKA, as well as the complications of therapy. Adequate intravascular volume is restored with an isotonic glucose-free solution, combined with exogenous insulin administration, commonly referred to as a “two-bag system.”<sup>571</sup> Regular insulin is given as an IV infusion of 0.1 Units/kg/h. The goal is to decrease blood glucose by 75 to 100 mg/dL/h. This infusion is continued until the blood glucose reaches 250 to 300 mg/dL, at which time 5% dextrose in normal saline (D<sub>5</sub>NS) is added to the infusate. This regimen of simultaneous glucose and insulin infusion can be continued until the patient can tolerate oral feedings and routine

subcutaneous insulin administration. Most clinicians continue the insulin infusion until the acidosis is nearly corrected. Potassium concentrations should be monitored closely. These children have total-body potassium depletion, but potassium should not be added to any infusion until there is urine output. The need for phosphate may be more theoretical than real, but in most situations, half the potassium is given as a phosphate salt. The severe metabolic acidosis is usually corrected with volume and insulin administration. The use of bicarbonate to correct acidosis is generally avoided because bicarbonate may precipitate or worsen the child's neurologic dysfunction. In severe DKA, the intracellular volume of brain cells is reduced by hyperosmolar dehydration. In an attempt to maintain their normal size, brain cells generate osmotically active idiogenic osmoles (e.g., inositol) that attract more water into the intracellular compartment. As systemic rehydration and correction of the hyperosmolar state begin, the brain cells may swell until the idiogenic osmoles are metabolized or cleared. Consequently, rapid correction of osmolarity can cause significant brain edema<sup>572</sup> and may also worsen the neurologic dysfunction, which may require invasive neuromonitoring.<sup>546</sup> The pH of the brain is determined by the CSF bicarbonate level and by the CO<sub>2</sub> content; the CSF CO<sub>2</sub> content equilibrates much more rapidly with the vascular space than bicarbonate does. Therefore, correcting the systemic acidosis decreases the level of hyperventilation and causes a rise in PaCO<sub>2</sub>; if this rise is precipitous, the CSF acidosis could worsen before the bicarbonate equilibrates with CSF. Because rapid correction of pH is problematic, bicarbonate administration is not advocated in DKA unless cardiovascular instability is present. Even then, the doses administered are small. Unfortunately, despite very careful and slow correction of the hyperosmolar and acidotic state, hyperosmolar coma and fulminant brain edema can occur.<sup>573</sup> The pathophysiology of brain swelling in DKA is poorly understood. Subclinical brain swelling may be relatively common in children with DKA.<sup>574</sup> If the swelling is significant, mannitol should be administered immediately and therapy for intracranial hypertension begun. The goal is to prevent secondary injury to the brain.

## GASTROINTESTINAL SYSTEM

GI problems in the ICU include organ dysfunction and failure from acquired disease and from congenital anatomic malformations and dysfunction. Delivery of adequate nutrition to critically ill patients is necessary.

### Structural and Functional Development of the Intestine

Knowledge of fetal midgut development makes it easier to understand a number of severe congenital anomalies. Although the intestine begins as a hollow tube, it is occluded by 7 to 10 weeks' gestation by rapidly growing epithelial cells. The lumen is later reconstituted when vacuoles within the epithelial cells coalesce. Some of the neonatal intestinal atresias are the result of abnormalities of this recanalization process. At 3 to 10 weeks' gestation, the midgut lies outside the abdominal cavity, with only the hindgut fixed in

the left side of the abdomen. The gut rotates 270 degrees counterclockwise and reenters the abdominal cavity at 10 weeks' gestation. If the midgut fails to migrate back into the abdominal cavity, an omphalocele occurs. Abnormalities in midgut rotation result in abnormal intraabdominal relationships, the most important being malrotation and volvulus of the intestine.

### Development of the Liver

The liver begins as an outgrowth of the foregut at approximately 3 weeks' gestation. During fetal life, it is relatively large in comparison to the adult liver. Although the fetus relies on the maternal liver and placenta for detoxification and excretory function in utero, the fetal liver is necessary for both prenatal and postnatal survival. As early as 10 to 12 weeks' gestation, the fetal liver is involved in glucose regulation, protein synthesis, and lipid synthesis, and is capable of some drug metabolism. The fetal liver contains approximately three times the amount of glycogen as the adult liver, but the glycogen is nearly completely released within hours of birth to compensate for interruption of the placental supply of nutrients.<sup>575</sup> It takes several weeks for the newborn to reestablish the store of liver glycogen, putting the infant at risk for hypoglycemia during this vulnerable period.

### Congenital Malformations

Gross anatomic malformations are usually diagnosed during the first few days of life. Some, such as omphalocele, gasteroschisis, diaphragmatic hernia, and imperforate anus, are apparent on the initial physical examination. Others manifest themselves in the first few days of life as failure to feed enterally, intestinal atresia, microcolon, tracheoesophageal fistula, and meconium ileus. Other malformations present difficult diagnostic and therapeutic dilemmas after the neonatal period. Specific clinical problems are discussed in the following sections.

**Intestinal Malrotation and Midgut Volvulus.** Malrotation of the intestine is caused by incomplete rotation of the fetal midgut when the gut migrates into the abdominal cavity. This abnormal rotation can cause partial or complete duodenal obstruction by peritoneal (Ladd) bands or, more importantly, midgut volvulus. The midgut (duodenum to transverse colon) and its vascular supply hang on a single pedicle; if the pedicle twists, the entire midgut may infarct. Infants with omphalocele almost invariably have associated malrotation of the gut. Symptomatic infants and children have signs of high intestinal obstruction (bilious vomiting) or signs of an acute abdomen, intestinal perforation, and sepsis. Treatment is surgical reduction and fixation of the volvulus and resection of nonviable bowel. Postoperative respiratory support and total parenteral nutrition are often necessary in infants who were severely compromised before surgery.

**Meckel Diverticulum.** Meckel diverticulum represents persistence of the omphalomesenteric or vitelline duct and is brought to the attention of the physician because of painless lower GI bleeding. The bleeding site is due to ulceration of the bowel mucosa caused by secretion of gastric acid.

Although usually self-limited, massive and life-threatening hemorrhage has been reported.<sup>576</sup> The diagnosis can be difficult to make because it is often one of exclusion. The technetium pertechnetate isotope scan demonstrates gastric mucosa in the diverticulum. Therapy is supportive, but particular attention must be paid to blood replacement. Definitive therapy is surgical resection.

**Hirschsprung Disease.** Hirschsprung disease (congenital aganglionic megacolon) is characterized by the absence of parasympathetic ganglion cells in the rectum and colon and occasionally in the small bowel.<sup>218</sup> Lack of ganglia cause narrowing of the distal bowel and distention of the normal proximal bowel. The clinical symptoms can be relatively minor, with abdominal distention and stool retention, or severe, with toxic megacolon, peritonitis, and intestinal perforation. Toxic megacolon is usually manifested in younger children; reported mortality rates are as high as 75% with toxic megacolon. The diagnosis of Hirschsprung disease is occasionally made by the history and physical examination. A barium enema reveals a narrowed segment with ballooning of the proximal part of the bowel. The definitive diagnosis is made by finding no ganglion cells on rectal or colon biopsy (or both). Treatment of toxic megacolon is both supportive (volume re-expansion and antibiotic administration) and definitive (surgical decompression via colostomy).

**Other Intestinal Disorders.** Intestinal disorders can cause bleeding, obstruction, or inflammation, and there can be secondary problems such as malabsorption and bowel perforation. GI bleeding in children is caused by inflammatory diseases (gastritis), ulcers, varices, or vascular malformations. Although ulcer disease is an uncommon initial complaint in pediatric patients, stress gastritis or stress ulcers occur in critically ill children. Prophylactic antacids or an H<sub>2</sub> antagonist should be considered. Bowel obstruction can be caused by intussusception, twisting of the bowel around congenital or postsurgical bands, and twisting of the bowel on itself (volvulus). Intussusception is relatively common in the pediatric age group and usually occurs in the distal part of the ileum. In only a few cases can a leading point, such as a polyp or localized edema (as seen in Henoch-Schönlein purpura), be identified. Treatment of intussusception can be surgical or, in patients with no evidence of necrotic bowel, with barium, air, or saline enema.<sup>577</sup> Inflammatory bowel diseases include Crohn disease and regional enteritis.<sup>578</sup> Infectious agents to be considered include *Salmonella*, *Shigella*, and *Yersinia*. These patients often have diarrhea, malabsorption (especially lactose intolerance), and bloody diarrhea. They also can have a toxic acute abdomen.

**Necrotizing Enterocolitis.** Necrotizing enterocolitis (NEC) is an often fulminant neonatal disease characterized by ulceration and necrosis of the small bowel and colon. Its cause is unknown but is probably multifactorial. Prematurity is the greatest risk factor for NEC. It is probably due to a combination of intestinal ischemia, oral feeding, and pathogenic organisms. Umbilical artery catheters,

perinatal asphyxia, RDS, and persistent patent ductus arteriosus have all been implicated.<sup>579</sup> The incidence of NEC is on the rise, with 1% to 5% of infants in neonatal ICUs affected. The most common initial signs are feeding intolerance, abdominal distention, and bloody stools. Intestinal obstruction, bowel perforation, and sepsis may follow. Treatment consists of withholding enteral feeding, nasogastric decompression, IV fluids, hemodynamic support, administration of appropriate antibiotics, and surgical exploration if there is evidence of an acute abdomen with free air. Peritoneal drainage may be helpful for very-low-birth-weight babies and for those in extremis.<sup>580</sup> Total parenteral nutrition is frequently required for several weeks, and intestinal obstruction may occur weeks to months after a relatively benign course.<sup>581</sup>

**Hepatic Failure.** Hepatic failure occurs with chronic or acute liver disease. Chronic liver failure can be caused by biliary atresia, inborn errors of metabolism (tyrosinosis, Wilson disease, galactosemia, cystic fibrosis), or chronic inflammatory hepatitis. Children with chronic disease often have signs and symptoms of synthetic dysfunction (malnutrition, hypoalbuminemia, abnormal coagulation), degradation dysfunction (icterus and hyperammonemia), and portal hypertension (hypersplenism and varices). Acute liver failure is most commonly caused by infectious hepatitis A and B. Evidence of bleeding, edema, and other organ dysfunction, including identification of liver and spleen size, is sought on physical examination. Laboratory evaluation should include screening for synthetic function (albumin, prothrombin time [PT], partial thromboplastin time [PTT]), degradation products (bilirubin, ammonia), and liver enzyme concentrations. Hepatic ultrasound, radiographic contrast studies, and liver biopsy are indicated on an individual basis. Life-threatening complications of liver failure include acute bleeding and cardiovascular compromise (from massive intravascular hypovolemia as a result of fluid shifts) and intracranial hypertension from toxic encephalopathy. Treatment is expectant and supportive. A 10% dextrose infusion will provide adequate carbohydrate intake. Low-protein diets minimize ammonia production. Coagulation is supported with vitamin K, fresh frozen plasma, and platelets as required. Plasmapheresis with fresh frozen plasma and platelets improves coagulation and maintains normovolemia. Oral lactulose and neomycin enemas decrease the enterohepatic cycle of ammonia production and absorption.<sup>582</sup> Cardiovascular and respiratory function should be monitored closely and supported as required. The development of intracranial hypertension must be anticipated. Serum ammonia levels are used to monitor neurologic dysfunction,<sup>582</sup> but it is unknown whether ammonia is the primary CNS toxin or whether it is just one of many chemical markers. Steroids have been used for some forms of inflammatory hepatitis. Exchange transfusions and plasmapheresis have been used to decrease the toxin load,<sup>583</sup> but there is no strong evidence that such measures reduce morbidity and mortality.<sup>584</sup> Patients with certain forms of acute hepatic failure, including those resulting from toxic and infectious causes, may be considered candidates for liver transplantation.<sup>228,585</sup>

**Extrahepatic Biliary Atresia.** Extrahepatic biliary atresia occurs once in every 8000 to 10,000 live births.<sup>586</sup> The extent of atresia differs from patient to patient and involves variable degrees of obstruction or discontinuity of the biliary tree between the duodenum and the proximal branches of the hepatic ducts. Treatment is surgical (jejunal Roux-en-Y and portoenterostomy) and is tailored to the amount of extrahepatic bile duct present. The Kasai procedure is most successful in patients operated on before they are 6 to 9 months of age. However, this procedure is associated with many acute and chronic complications, including hepatic failure, ascending cholangitis, and cirrhosis with portal hypertension and varices. Despite these complications, the Kasai procedure persists because there are not enough suitable donor organs.<sup>587</sup>

**Liver Transplants.** Improved immunosuppressive drugs and surgical techniques have increased the success of liver transplantation (see Chapters 16, 60, and 61). For transplantation to be successful, the perioperative and postoperative periods require a coordinated approach among surgery, gastroenterology, anesthesia, immunology, and the ICU staff. Most of the clinical issues that arise can be anticipated. Large blood losses occur and massive replacement therapy is required in the operating room. Accordingly, intravascular volume status, renal status, and hematology/coagulation profiles must be closely monitored. The immunosuppression required puts the patient at risk for infection with both “normal” and opportunistic organisms. Surveillance cultures and early aggressive antibiotic therapy are indicated. Systemic hypertension, which appears to be unrelated to elevated CVP or pulmonary capillary wedge pressure, is due to the antirejection drugs. Many patients require aggressive antihypertensive therapy (hydralazine, diazoxide, captopril).<sup>588,589</sup>

### Enteral and Parenteral Nutrition for the Critically Ill Child

Nutritional support of a patient in the PICU may be less of a concern to health care providers when there are neurologic, respiratory, and cardiovascular issues to be addressed. However, not addressing the nutritional needs of our patients misses an important opportunity to improve their care and outcome. The active area of research is to demonstrate the benefits of early enteral nutrition (EEN) in critically ill children. There are the potential benefits of reduced translocation of gut bacteria, reduced constipation, and reduced infectious risks as compared with parenteral nutrition. Research by Khorasani et al.<sup>590</sup> published in 2010 in a single center study showed decreased mortality in children with burns who received EEN 8.5% as compared with late enteral nutrition 12%. In a 2012 international multicenter cohort study published by Mehta et al.,<sup>591</sup> there was a lower 60-day mortality associated with a higher percentage of goal energy intake via an enteral route. The consecutively enrolled cohort consisted of 500 children ages 1 month to 18 years who required mechanical ventilation greater than 48 hours in a pediatric ICU. Their study further demonstrated that mortality was higher in the patients who received parenteral nutrition.<sup>592</sup> This research demonstrating EEN improves outcome in critically ill children is further supported by the 2013 work of Mikhailov

et al.<sup>592a</sup> The study was a multicenter retrospective study with 12 participating centers. Pediatric patients 1 month to 18 years were included if they had a PICU length of stay  $\geq$  96 hours and a total of 5105 patients were identified. The study defined EEN as obtaining 25% of goal calories enterally within the first 48 hours of ICU admission. The study noted that children who received EEN were less likely to die as compared with those that did not (odds ratio, 0.51; 95% CI 0.34-0.76;  $P = .001$ ). This was after adjusting for severity of illness, age, and participating center. There were nonsignificant increases in length of stay and duration of mechanical ventilation.

Given the increasing evidence supporting EEN, we should be considering daily whether it is possible to start feedings. We should also consider placing feeding tubes beyond the pylorus to that enteral nutrition can proceed during ICU procedures. Mehta et al.<sup>592</sup> showed significant interruptions in enteral feedings even after they had been initiated. Feeds were stopped on average for 2 days in 71% of their patients. If it is not possible for each of us to individually advance feedings, there is good information that adoption of a feeding protocol in an ICU setting increases goal enteral nutrition.<sup>593</sup> It is possible that between 25% and 30% of the patients admitted to the PICU are malnourished.<sup>592</sup> Smaller children and those with chronic illness have limited energy reserves, and early enteral feeding should be targeted. If enteral nutrition is not a possibility, parenteral should be considered, but it does carry risks. Higher dextrose solutions increase the risk of phlebitis or complications, should there be an infiltrate of a peripheral IV catheter. Higher dextrose concentrations might also require placement of central venous catheters, which carries risks during placement and ongoing risks of infection. Additional risks of parenteral nutrition include infection, cholestasis, hepatic stenosis, electrolyte disturbance, and elevated triglycerides. Until there is further evidence showing harm for malnourished children, initiation of parenteral nutrition should be considered if enteral feeding is not an option.

### Hematology

Hematologic emergencies in the ICU include abnormalities in coagulation, immunity, and RBC mass. They can be primary isolated defects, or they can be caused by multiorgan system failure. The immune system is discussed in the section on infectious disease.

**Coagulation System.** Normal clotting includes initial platelet hemostatic plug formation and fibrin production (intrinsic or extrinsic pathways). For both to occur, platelets, coagulation factors, and an intact blood vessel are essential. Neonates have a number of measurable coagulation abnormalities that rarely have clinical manifestations. Full-term and most preterm infants have normal platelet-vessel interaction, but platelet aggregation is transiently impaired. In addition, many coagulation factors show decreased activity or concentration in the fetus and newborn. Of greatest importance are the vitamin K-dependent factors: factors II, VII, IX, and X. These factors are low at birth and decrease to even lower levels during the first week of life unless vitamin K is administered. The amounts of factor V and VIII are close to adult levels in all but the most premature of infants. Although routine screening tests for coagulation activity

are prolonged in infants, the newborn's blood clots more rapidly in vitro because neonates lack sufficient naturally occurring protease inhibitors, principally antithrombin III.

**Transfusion Therapy.** Many PICU patients require blood transfusions during their hospitalization (Table 79.11). Decreased RBCs may be secondary to decreased production or ongoing losses frequent lab testing. Decreased platelets may be secondary to decreased production or sequestration in the spleen. Thrombocytopenia from frequent lab testing may be less common. Decreased production of coagulation factors in the setting of liver failure may predispose patients to further blood loss. The transfusion of blood products in any setting carries associated risks. Transfusion reactions can be separated into nonimmune and immune mediated problems. The nonimmune reactions include transmission of viral or bacterial infections through blood components, circulatory overload, coagulopathy, hypothermia, and changes in electrolytes. Hemolysis of erythrocytes in packed red blood cells (PRBC) is increased by prolonged storage. The potassium levels can be quite elevated in older units. In trauma or situations of acute blood loss, rapid transfusion of RBCs can lead to hyperkalemia. This is typically not a problem in an ICU setting, where PRBC are transfused over 2 to 4 hours. The immune mediated reactions include intravascular and extravascular hemolysis. Hemolytic transfusion reactions can be severe and life threatening. Cross-matching blood products can reduce hemolytic reactions, but there must also be careful identification of the patient and the blood unit to be transfused. Nonhemolytic immune-mediated reactions include febrile reactions, mild allergic, anaphylactic reactions, and transfusion-related acute lung injury (TRALI).

**Transfusion Related Acute Lung Injury.** TRALI previously may have been an under reported complication of transfusion, but awareness is improving. The number of studies on TRALI in pediatric ICU patients is increasing.<sup>594-600</sup> The diagnosis TRALI following a blood transfusion relies on excluding other causes of pulmonary edema. This includes eliminating volume overload, sepsis, and cardiogenic pulmonary edema as causes of the patient's pulmonary edema. It is proposed that there is a two-hit model of TRALI. The first hit is an underlying component of inflammation in the lungs. The second hit is transfusion of a

blood product that results in the development of TRALI. It is still not clear whether the damage is caused by the presence of neutrophils, HLA antibodies, or biologically active lipids present in older blood units. A study by Church et al.<sup>601</sup> showed an association with increased mortality for pediatric patients with Acute Lung Injury who received fresh frozen plasma. Due to the ALI, this is a group that already has the first hit. The mortality association was independent of the severity of hypoxemia, the presence of disseminated intravascular coagulopathy, or the presence of multiple organ dysfunction syndrome. Blood transfusion has associated risk, and these risks should be considered prior to any transfusion. In some clinical scenarios, pediatric patients will tolerate a greater degree of anemia than we would have previously considered. In 2007 Lacroix et al.<sup>602</sup> with the Transfusion Requirements in Pediatric Intensive Care Units (TRIPICU) study demonstrated that by adopting a restrictive transfusion strategy, they were able to reduce transfusion of PRBCs to PICU. A hemoglobin threshold of 7 g was targeted in one group as compared with 10 g in other. In the restrictive threshold group, there was a 44% reduction in PRBC transfusion without an increase in adverse outcomes. This information may not be able to be applied to all groups in the ICU, such as those with ongoing blood loss. The patients in the TRIPICU study did not have a blood pressure lower than 2 SD below an age appropriate mean, and they did not require increasing doses of inotropic medication. Subgroup analysis of the original TRIPICU study in general pediatric surgery<sup>603</sup> and cardiac surgery patients did not show a significant difference in the development of multiple organ dysfunction syndrome.

**Coagulopathy.** Coagulation defects can occur due to a number of underlying conditions in PICU patients, such as sepsis, trauma, malignancy, pancreatitis, and liver failure. As a reminder, the PT tests the extrinsic and common pathways of coagulation. The PT is prolonged in liver failure, vitamin K deficiency, and DIC. The activated partial thromboplastin time (aPTT) tests the intrinsic and common pathways of coagulation. The aPTT is prolonged in liver failure, hemophilia A, Von Willebrand disease, and DIC. One major concern in a PICU setting is that the underlying inflammatory state in some patients can activate coagulation and inhibit the natural anticoagulation mechanisms. This is the basis for disseminated intravascular coagulation. In 2001, the International Society of Thrombosis and Hemostasis<sup>604</sup> published a DIC scoring system. Their DIC score uses platelet count, fibrin-related markers, PT, and fibrinogen. They separated DIC into nonovert DIC and overt DIC. In nonovert DIC, the balance of hemostasis is stressed by inflammation or noninflammatory disorders of the microvasculature stress hemostasis, but compensation is maintained. In overt DIC, the hemostatic system is can no longer compensate. A DIC scoring system such as this allows for ongoing research and a measure of response to therapy. In 2009, Khemani et al.<sup>605</sup> demonstrated the association between an elevated DIC score and mortality in 132 PICU patients with sepsis or shock. There are a maximum of 8 total points on the DIC score. Lower platelet counts and fibrinogen, prolongation of the PT, and evidence of fibrin degradation all are given points. There was a 50% mortality for patients with overt DIC (DIC score  $\geq 5$ ). For patients with a DIC score of less

**TABLE 79.11** Blood Component Therapy

Blood Component	Dose	Comments
Packed red blood cells	10-20 mL/kg	Raises hemoglobin 2-4 g/dL
Random donor platelets	1 unit/10 kg or 5-10 mL/kg	Pooled units from multiple donors
Apheresis platelets	10 mL/kg	Donation from single donor
Fresh frozen plasma	10-20 mL/kg	Provides 20%-30% of coagulation factors
Cryoprecipitate	1 unit/10 kg	Significant amount of fibrinogen (50-80 mg/dL)

than 5, the mortality was 20%. This association between elevated DIC score and mortality remained even when controlling for severity of illness and/or use of inotropic medications. The treatment of DIC is to treat the underlying condition which is causing imbalance of the coagulation system. A future goal of research will be to study patient outcomes as DIC is corrected with FFP. As Church et al.<sup>601</sup> found an increased mortality associated with FFP transfusion, it is not clear what the balance will be between the risk of DIC or the risk of transfusion.

**Sickle Cell Disease.** Hemoglobin S or sickle cell trait is the most common of the hemoglobinopathies. There are also significant regional variations on the concentration of patients with different thalassemias. Hemoglobin S is caused by a point mutation in the beta-chain at codon position 6, which results in a substitution of valine for the normal glutamine. Hemoglobin S is formed from the combination of an abnormal beta chains with the valine with normal alpha chains. When there are two copies of the abnormal gene present, hemoglobin SS or sickle cell disease is produced. Complications from sickle cell disease (Hb SS) cause the most frequent PICU admissions of the hemoglobinopathies. Deoxygenation of the Hb SS erythrocytes causes intracellular hemoglobin polymerization, which leads to loss of deformability and changes in the erythrocyte morphology. In a deoxygenated state the abnormal erythrocytes change from a biconcave configuration to the classic sickle cell shape. The abnormal erythrocytes have a much shorter life-span and hemolyze more readily. In turn, patients with sickle cell disease have a chronic severe hemolytic anemia.

**Sickle Cell Crisis.** There are three types of sickle cell crisis that can occur: hemolytic, aplastic, and vaso-occlusive. A hemolytic crisis is characterized by increased hemolysis, which results in an acute drop in hematocrit and hemoglobin. This is typically accompanied by a significant increase in red cell production or reticulocytosis. At an aplastic crisis there is a drop in hematocrit and hemoglobin, but there is no associated reticulocytosis. The production of red cell precursors in the bone marrow has slowed or stopped. The cause of an aplastic crisis is often infectious with greater than 90% of cases due to parvovirus B19. A vascular occlusive crisis is what is typically thought of as the classic sickle cell crisis. A vascular occlusive crisis may be brought on by infection, dehydration, acidosis, or hypoxia. The erythrocytes assume a sickled configuration, which blocks small vessels leading to infarction. The infarcts can occur in any organ but are frequent in the lungs, kidney, bones, skin, spleen, eyes, and CNS.

**Acute Chest Syndrome.** A vascular occlusive crisis in the lungs leads to acute chest syndrome (ACS). Acute chest syndrome is leading cause of death and the second most common complication in sickle cell disease. ACS is defined as a new pulmonary infiltrate on a chest radiograph, in association with a fever, respiratory symptoms, or chest pain. There is great variability to the clinical course in ACS. The National Acute Chest Syndrome Study Group<sup>606</sup> reported a multicenter showing almost 50% of patients later diagnosed with ACS present initially with

another symptom, mostly typically being pain. The presence of a pulmonary fat embolism is frequently reported and is associated with a particularly severe course. The cause of the pulmonary fat embolism is most likely bone marrow necrosis with release necrotic bone marrow fat into the blood stream. A common etiology of ACS is infection. *Chlamydia pneumonia* and *mycoplasma* are the most commonly identified pathogens. The goal for management of ACS is early recognition. As children with sickle cell disease may have few initial symptom, there should be a high index of suspicion. All febrile children with sickle cell disease should have a chest radiograph obtained. If there is any positive radiologic findings, therapy should begin immediately. Initial antibiotic treatment is cefuroxime or cefotaxime with a macrolide. The patient should be adequately hydrated. The patient should be observed closely, and if the patient becomes fluid overloaded, diuretic therapy should be started. Patients should receive oxygen therapy even if there are normal oxygen saturations. Incentive spirometers should be used by every child who is able. There should be consideration given to the use of bronchodilators. Every effort should be made to see that pain is adequately controlled. A simple red cell transfusion may be helpful if the patient is anemic, but an exchange transfusion may be needed. There is some regional variation in this practice. The reason to perform an exchange transfusion is that as the hemoglobin rises the blood viscosity will increase. Further sickle cell blood has a very high viscosity in the deoxygenated state. Performing a red cell exchange can reduce blood viscosity as well as improve oxygenation.<sup>604</sup> An exchange transfusion may improve perfusion in the microvascular perfusion, as well as cause a reduction in inflammatory mediators. In patients with sickle cell disease, red cell exchange has been shown to reduce white blood count, platelet count, and soluble vascular cell adhesion molecule-1 in patients. However, there was no effect on interleukin-1 $\alpha$ , interleukin-1 $\beta$ , interleukin-8, or tumor necrosis factor- $\alpha$ , and the reductions that occurred were short-lived. In the National Acute Chest Syndrome Study Group<sup>607</sup> publication, 13% of patients required mechanical ventilation, and in this group that required intubation, the mortality was 19%.

**Neurologic Complications.** Exchange transfusion has a vital role in the treatment of neurologic complications from sickle cell disease. In a population of patients with sickle cell disease, at less than 20 years of age the incidence of stroke was measured at 0.44 per 100 patient-years.<sup>608</sup> Studies have been performed to identify at risk patients and initiate therapy prior to the development of stroke. The Stroke Prevention Trial in Sickle Cell Anemia (STOP) was to evaluate whether chronic transfusion therapy could prevent an initial stroke in children with sickle cell disease. Transcranial Doppler was used to identify patients at increased risk for stroke. A hemoglobin S concentration of less than 30% was maintained in the study group.<sup>609</sup> The risk for stroke development was reduced by 90% in the chronic transfusion group, as compared with the patients receiving standard of care. The trial was stopped 16 months early due to these findings. Chronic transfusion therapy does carry the long-term side effects of alloimmunization and iron overload.<sup>610</sup> The information available would indicate that for a child

with sickle cell disease and an acute neurologic change exchange transfusion should be performed. While there is a significant need with ACS or neurologic change, for an exchange transfusion, it is not without risks. Depending on regional variation, central venous or arterial access is needed. Patients need to be followed closely for the development of fluid overload or hypovolemia during the exchange. There are the risks of blood products. Small children are at risk for hypothermia if the blood is not warmed. The best location and method to handle exchange transfusion will depend on the resources of the ICU, blood bank, and hematology department.

**Acquired Disorders.** A variety of circumstances can impair the production of coagulation factors. The vitamin K-dependent factors are most commonly affected. These factors are decreased with liver disease, warfarin therapy, and malabsorption syndromes secondary to either bowel disease or altered bowel flora caused by long-term antibiotic therapy. In addition, untreated neonatal vitamin K deficiency results in hemorrhagic disease of the newborn. In these disorders, the PT is prolonged and there are low levels of factors II, VII, IX, and X. Administration of vitamin K usually reverses these deficiencies, unless the synthetic function of the liver is markedly compromised.

Acquired platelet abnormalities include decreased production, increased destruction, and decreased function. Decreased production or hypoproliferative states include marrow diseases, such as leukemia and aplastic anemia, and the side effects of chemotherapeutic agents. Increased destruction can be immune mediated (i.e., idiopathic thrombocytopenic purpura<sup>611</sup>) or the result of consumption (i.e., microangiopathic states, HUS, or thrombotic thrombocytopenic purpura<sup>612</sup>). Finally, platelet dysfunction has been found with uremia and chronic polycythemia in patients with cyanotic heart disease.<sup>613</sup> Treatment of acquired thrombocytopenia includes platelet transfusions and, if possible, correction of the underlying disorder. Therapeutic splenectomy will increase platelet survival in some patients with severe immune-mediated diseases.

## Oncology

Over the past several decades, there has been significant improvement in survival of pediatric cancers. A great amount of information demonstrating this effect is available from the Surveillance, Epidemiology, and End Results Program at [www.seer.cancer.gov](http://www.seer.cancer.gov). Further, there has been an increase in the number and types of diseases treated with hematopoietic stem cell transplantation (HSCT). These facts have resulted in an increasing volume of oncology patients in the pediatric ICU. This patient population received very specialized, detailed care on specialized oncology wards or bone marrow transplant units. The care delivered in these areas as well as the strict isolation procedures employed there are difficult to replicate in other locations in the hospital. In an effort to keep oncology patients in oncology wards, some hospitals have policies allowing the use of low amounts of inotropic support in these areas—for example, dopamine up to 5 µg/kg/min. This may mean that some oncology patients are transferred to the ICU when they have exceeded this level of support. They may have sepsis and shock not responding

to fluid resuscitation and low inotropic support. Other patients may require respiratory support that cannot be delivered on the ward. Finally, there is early literature indicating that earlier initiation of CRRT to treat or prevent fluid overload<sup>614,615</sup> has benefits in HSCT, with other studies showing no benefit.<sup>616</sup> However, the positive literature has prompted earlier admission to the ICU for HSCT patients who become fluid overloaded. Overall, there is evidence showing improved outcomes for pediatric oncology patients requiring ICU care.<sup>617-620</sup> For patients following HSCT, after controlling for severity of illness, a temporal improvement in mortality is less evident.<sup>621</sup> Further, for patients requiring mechanical ventilation, the mortality is greater following HSCT compared with non-HSCT oncology patients.<sup>622</sup>

Due to the disease and therapy at times during their illness, oncology patients are profoundly immunocompromised. There is an increased risk of sepsis during periods of neutropenia. Fever may be the first indication of sepsis and studies have looked at predicting which patients will go on to be bacteremic.<sup>623,624</sup> The outcome of sepsis and oncologic disease is an ongoing concern. A study by Pound et al.<sup>617</sup> showed that ICU mortality for patients with septic shock was not significantly different between oncology patients 15.9% compared with matched controls 11.6%. There was no significant survival difference between groups in the first 6 months following discharge from the ICU. A 2005 study by Fiser et al.<sup>620</sup> showed on overall mortality of 17% for pediatric oncology patients with severe sepsis. The mortality in the HSCT group (30%) was greater than the non-HSCT group (12%). For patients who required both mechanical ventilation and inotropic support there was a high mortality (64%).

## Leukostasis

Leukostasis (vascular obstruction) results from high viscosity caused by elevated cell counts or by the WBCs themselves. This syndrome is anticipated in patients with acute lymphoblastic leukemia when the WBC count exceeds 500,000 and in AML patients with WBC counts greater than 200,000/mm<sup>3</sup>. In AML, leukemic cells are less deformable than lymphoblasts, so a lower WBC count produces the same syndrome.

The brain and lungs are the two major target organs for leukostasis; vascular plugging and organ infarction are the usual manifestations. Initial symptoms include tachypnea, cyanosis, increased work of breathing, altered mental status, and focal neurologic deficits. Besides supportive therapy, reducing the circulating tumor load and viscosity are the primary goals of therapy. Leukapheresis and exchange transfusion transiently accomplish these goals. Cranial irradiation may reduce the CNS tumor load, and chemotherapy will interrupt cell production and possibly destroy circulating cells. The initial goal of chemotherapy is to stop cell production without producing massive cell lysis; this halts the increase in tumor load without causing a severe metabolic crisis before adequate perfusion is reestablished.<sup>625,626</sup>

## Tumor Lysis Syndrome

TLS is a metabolic crisis precipitated by acute lysis of a large number of tumor cells. Serum uric acid, potassium, and

phosphate concentrations are elevated; the elevated phosphate concentrations cause hypocalcemia. The hyperkalemia and hypocalcemia can be life threatening; increased uric acid may cause acute renal failure.<sup>627</sup> Therapy for TLS consists of alkalinization of urine, fluid administration, and diuresis. Before any chemotherapy is administered, the patient's renal function should be assessed. If renal function is normal, allopurinol or rasburicase therapy is begun. In most cases, this conservative approach of forced diuresis and allopurinol or rasburicase will prevent renal failure, but occasionally dialysis must be instituted. Indications for the initiation of dialysis include

1. Potassium greater than 6 mEq/L and rising despite resin exchange
2. Uric acid greater than 19 mg/L
3. Creatinine greater than 10 mg/L
4. Phosphorus greater than 10 mg/L or rapidly rising
5. Volume overload
6. Symptomatic hypocalcemia

### Mediastinal Mass

Children with a mediastinal mass and respiratory distress often complain of coughing, difficulty breathing, stridor, and shortness of breath. They prefer to sit upright and cannot lie supine. The chest radiograph usually shows a large mediastinal mass, often with obliteration or obscuring of the tracheal air column. These masses can also cause positional obstruction of vascular structures such as the superior vena cava or a pulmonary artery. Lam et al. indicate that clinical presentation is often nonspecific or often times incidental, and that patients with airway compromise often times also exhibit symptoms of superior vena cava syndrome.<sup>628</sup> These patients are often referred to as having *critical mediastinal mass syndrome* and require the care of an experienced multidisciplinary team. These tumors can be malignant (87% Hodgkin and non-Hodgkin lymphoma) or benign; the prognosis and therapy rely on adequate diagnosis, which is best made by obtaining a tissue sample before treatment is begun.<sup>629</sup> However, obtaining a sample of the mediastinal mass may require anesthesia and surgery, and the airway must be manipulated and instrumented. All these maneuvers may cause the patient to die. Local anesthesia with fine-needle biopsy under radiographic guidance allows tissue sampling without anesthesia in some patients. Irradiation of the tumor before obtaining a tissue sample may reduce the size of the tumor and make biopsy easier and safer under anesthesia. Obstruction of the intrathoracic trachea is a major anesthetic risk for these patients; it is often impossible to maintain a patent airway when the patient lies supine, is deeply anesthetized, or is paralyzed with muscle relaxants.<sup>628,630</sup> However, the patient must cooperate sufficiently to perform the test, which is often difficult for them because of respiratory distress. Induction of anesthesia and tracheal intubation are usually done with the patient in the sitting position and breathing spontaneously. If the airway compromise is severe, the tumor should be irradiated and the child given steroids before a tissue diagnosis is made; however, these treatments could alter diagnosis and should be discussed with an oncology consultant prior to initiating. Sometimes, a peripheral node or mass can be biopsied under local anesthesia, or if the tumor

mass is very large, some of the tumor can remain outside the field of radiation. Sticker et al. report that in a single center review of 46 cases that patients with symptomatic anterior mediastinal mass underwent biopsy with general anesthesia while maintaining spontaneous ventilation without serious complications.<sup>630</sup> In summary, although diagnosis is the key to treatment of neoplastic disease, the risk associated with biopsy may far outweigh the benefit of tissue diagnosis.

## IMMUNITY AND INFECTION

### Empiric Antibiotic Coverage

It is difficult to make empiric recommendations for antibiotic coverage for the pediatric ICU. Antibiotic resistance may result from use of broad spectrum antibiotics without some degree of stewardship. Further, empiric antibiotics should be based on the susceptibility profile of the common bacteria within each hospital and patient population. In our practice, for patients presenting with sepsis, vancomycin and a third generation cephalosporin in combination are the antibiotics of first choice. This is due to a rising incidence of methicillin-resistant *Staphylococcus Aureus* (MRSA). To reduce the spread of MRSA, all patients are screened on admission for colonization and isolated if MRSA is found. Antibiotic coverage can be more specific and narrowed as culture results as well as sensitivities return. Likely the best recommendation to be made regarding empiric antibiotic coverage is to meet with the Infectious Disease Specialists and discuss the current hospital culture isolates and their antibiotic resistance. Decisions regarding empiric antibiotics are best made in advance of the situation.

### Prevention of Health Care–Associated Infections

The impact of health care–associated infections (HAI) on the medical system is significant and on the individual patient level can be deadly. A 2007 paper from Klevens et al.<sup>631</sup> estimated the number of HAIs in U.S. hospitals in the year 2002 at 1.7 million. Of these, 417,946 HAIs occurred among adults and children in an ICU setting. The estimated deaths associated with the HAIs in this time frame were 98,987. Likely the best thing we can do to protect our patients is to wash our hands or use alcohol-based gels and encourage others to do so. Encouraging others or providing a positive role model may have a larger impact than anticipated. A 2009 study by Schneider et al.<sup>632</sup> paired trainees who were critical care fellows or nurse orientees with senior supervisors and evaluated compliance with HH. In the control phase the senior supervisors were unaware of the study and had a HH compliance of 20%. The trainees that were being mentored had a HH compliance of 22%. When the senior supervisors were recruited into the study there was a HH compliance of 94%. The trainees who were still blinded to the study had an increase in the HH compliance to 56%. Certainly, it is anticipated that there will be better compliance with hand hygiene if health care providers know that they are being observed. Yet the Schneider study shows the importance of role modeling positive behavior. In our ICUs, we have ongoing audits of HH compliance. We ask our patients' parents to remind health care providers to wash their hands if they

have not done so. Although it may be difficult, we must be willing to remind others to wash their hands.

### Ventilator-Associated Pneumonia

Intubation and mechanical ventilation is necessary for patients with respiratory failure. Unfortunately, an ETT prevents airway protective mechanisms and this increases the risk of ventilator associated pneumonia (VAP). Patients mechanically ventilated who do not have a pulmonary infection may develop pneumonia and patients mechanically ventilated for pneumonia may develop a secondary infection. VAP can increase morbidity and mortality. A 2009 study by R. Srinivasan et al.<sup>633</sup> demonstrated that patients with VAP had increased length of mechanical ventilation, prolonged stays in the ICU, and more importantly a significant increase in mortality. There was 2.4% mortality in the patients who did not develop VAP as compared with 10.5% mortality in the patients who did. VAP has been defined as the new onset of a lower respiratory tract infection for patients who have required mechanical ventilation for greater than 48 hours. The diagnostic criteria includes a new infiltrate on chest radiograph, a positive respiratory culture, a low or elevated WBC count, and fever or instability in temperature.

In January 2005, the Institute for Healthcare Improvement (IHI) started the 100,000 lives campaign. The goal was to save the lives of 100,000 patients in a period of 18 months by six specific clinical interventions that were evidence based. They encouraged hospitals to deploy rapid response teams, deliver evidenced based care for acute myocardial infarction, prevent adverse drug events, prevent surgical site infections, prevent central line infections, and prevent VAPs. The last two incorporated the use of bundles or collections of scientifically grounded interventions that were implemented collectively. These interventions have been successful. From the VAP standpoint the pre-bundle VAP incidence for PICU patients was reported in 2002<sup>634</sup> as 11.6/1000 ventilator days. The VAP bundle has been tailored to pediatric patients,<sup>635</sup> and there have been significant improvements in VAP incidence. In a 2009 study showing the benefit of bundle implementation, Bigham et al.<sup>636</sup> showed a significant reduction in VAP incidence from 5.6 to 0.3 per 1000 ventilator days. This was a single center study that also showed a reduction in length of mechanical ventilation, length of stay, and mortality. This positive benefit of bundle initiation has been shown in other pediatric studies as well.<sup>637,638</sup>

In an effort to reduce a new bacterial infection while mechanically ventilated, the components of the VAP bundle aim to reduce bacterial colonization and prevent aspiration of contaminated secretions. To reduce the amount of bacteria present in the mouth and sinuses, mouth care is performed with a chlorhexidine rinse every two to four hours. Several things are done to reduce the risk of aspiration of contaminated secretions. One is to suction the oropharynx prior to suctioning the ETT or deflating the ETT cuff. A second is to drain the condensation that occurs in the ventilator tubing every two to four hours and prior to repositioning the patient. This should be done without disconnecting the ventilator circuit. A third is to use inline suction catheters such that the ETT can be suctioned without disconnecting the ventilator circuit. Finally, by maintaining the head of

the bed greater than 30 degrees, there is a decreased risk of secretions in the ventilator tubing draining passively into the ETT.

We have found that the measures included in a VAP bundle are not difficult to perform and become routine practice quite quickly. More interesting is synergy that occurs with a bundle in that the impact of the combined interventions seems to be greater than any individual component. A strong adherence to a bundle of preventive measures has also been significantly helpful in the prevention of blood stream infection due to the presence of a central line.

### Catheter-Associated Blood Stream Infections

There is a significant increase in hospital stay, morbidity, mortality, and costs with the development of catheter associated blood stream infections (CA-BSI). In a prospective study performed in a pediatric cardiac ICU Abou et al.<sup>639</sup> showed 11% mortality in patients who developed a blood stream infection as compared with 2% mortality in patients who did not. It has been said by many that the best way to reduce a CA-BSI is to never place a central venous catheter. There is benefit to continually reviewing a patient's requirements for central venous access and when possible only using peripheral catheters. Unfortunately, there are many instances such as the need for vasoactive medications, where central venous catheters cannot be avoided. The implementation of bundles to care for central venous catheters can significantly reduce the development of blood stream infections and reduce the mortality and morbidity for each patient.

Implementation of preventive bundles during the insertion of and ongoing maintenance of central venous catheters will reduce infections. In a 2010 study<sup>640</sup> in 29 PICUs, there was a 43% reduction in the development of CA-BSI when bundles were used. These results are sustainable and continue to improve. The 2011<sup>641</sup> follow-up by the same group showed a further reduction in the incidence of CA-BSI. The bundle can be broken down into two parts: central line insertion and maintenance. During the insertion of the central venous catheter the goal of the bundle is to maintain complete sterility of the field. Chlorhexidine is used as the skin prep for patients greater than 2 months of age. All people in the room wear hats and masks. The persons performing the procedure wear these as well, along with a sterile gown and gloves. A large sterile barrier covering the entire bed is used. The second phase of the bundle is ongoing maintenance of the central venous catheter. There are strict guidelines for the care of the IV tubing, hub, and catheter insertion site. When dressing changes are performed, sterile gloves are used and the area is scrubbed for 30 seconds with chlorhexidine; then it is allowed to air dry for 30 seconds. Strict adherence to the same maintenance guidelines throughout the entire hospital is necessary to prevent CA-BSI. In many institutions, the number of infections has dropped so low that each event can be individually reviewed.

### Urinary Tract Infection

Catheter-associated urinary tract infections CA-UTI is the most common health care related infection. Removing a bladder catheter if it is not needed can significantly reduce the risk of developing a urinary tract infection. In some

cases, the catheter cannot be removed and efforts should be made to prevent infection. Institution of a bladder care bundle as a quality improvement measure can significantly reduce infection rates. In a 2013 study by Esteban et al.,<sup>642</sup> implementation of quality improvement interventions decreased the number of catheter-associated urinary tract infections from 23.3 to 5.8 per 1000 urinary catheter days. The goals of a bladder catheter bundle are to reduce the bacterial colonization and to reduce the reflux of urine back into the bladder. Catheters are inserted in a sterile fashion, and periurethral cleaning is performed with a chlorhexidine cloth at least once per shift. To prevent reflux, the collection bag is always kept below the level of the bladder and is drained completely or clamped prior to moving the patient.

### Infections in the Newborn

Neonates with developmental immunologic deficiencies have increased susceptibility to infection. Depressed cell-mediated immunity makes the fetus and infant more susceptible to viral and fungal infection. In addition, infants have depressed B-cell function and diminished production of immunoglobulins. The latter is partially offset by increased maternal immunoglobulin G (IgG). By 2 to 3 months of age, which is before infants can adequately produce their own antibodies in sufficient quantity, the level of maternal antibodies reaches a nadir.<sup>643</sup> The time during which the circulating antibody concentration is low is a time when the risk for infections is increased. Perinatal infections are either congenitally or postnatally acquired. Congenital infections occur with prenatal exposure to viral, protozoal, or rarely, bacterial pathogens. Common diseases include the TORCH infections: *Toxoplasma gondii* (T); "other" (O), including human immunodeficiency virus, syphilis, and tuberculosis; rubella (R); cytomegalovirus (C); and herpes simplex virus type 2 (H). Only rarely do these infections cause overwhelming sepsis, but they can be confused with bacterial infection when profound CNS depression, circulatory collapse, or thrombocytopenia occurs. When a TORCH infection develops in the first trimester of pregnancy, it causes fetal wastage or major organ malformation. Premature infants have a high incidence of acute infections in the newborn period. Regardless of gestational age, the signs and symptoms of infection are often subtle. Therefore, a very high index of suspicion and low threshold for diagnosing and treating infection are required.<sup>644</sup> Box 79.5 lists the common signs and symptoms of neonatal sepsis. The most common acquired pathogens are those that colonize the mother's genital tract: group B streptococci, *E. coli*, *Listeria monocytogenes*, and herpesvirus. Herpes is such a fulminant infection in neonates that the presence of active herpes lesions in the birth canal is an indication for cesarean section, although this may not prevent herpes in all children. Group B *Streptococcus* is the most common bacterial pathogen that causes neonatal sepsis. Infection with group B streptococci is manifested as severe cardiorespiratory instability and meningitis in 30% of cases. By 2 to 3 weeks of age, this organism is more commonly associated with meningitis and less commonly with pulmonary disease. Whenever sepsis is suspected, cultures of blood, urine, and CSF should be obtained. Because it is difficult for the physician to localize the infection in an infant, repeated complete

### BOX 79.5 Common Signs and Symptoms of Neonatal Sepsis

Temperature instability (hypothermia and hyperthermia)  
Lethargy and poor feeding  
Respiratory distress and apnea  
Hypoglycemia and metabolic acidosis  
Poor cutaneous perfusion, hypotension  
Rashes or petechiae  
Seizures

sepsis workups are often required. When appropriate cultures are obtained, treatment with ampicillin and an aminoglycoside, such as gentamicin, is usually begun until specific bacteriologic information becomes available. Only about 50% of neonates thought to be septic have positive cultures.

## PEDIATRIC TRAUMA

### Prenatal and Perinatal Injuries

Perinatal trauma occurs before or immediately after birth (also see Chapter 77). The most common prenatal injuries are due to maternal gunshot wounds and blunt trauma. Fetal mortality in both cases is at least twice that of the mother,<sup>645</sup> with fetal death being attributable to maternal shock and fetal oxygen deprivation rather than direct injury. Birth injuries occur more commonly in large full-term infants and in infants born by breech presentation. Injuries to the head include linear or depressed skull fractures, cephalohematomas, subdural or subarachnoid hematomas, and intraparenchymal or intraventricular hemorrhage. Intracranial injuries can increase ICP and cause cerebral ischemia, neurologic injury, and death. Injury to the sternocleidomastoid muscle may cause torticollis; traction on the neck may transect the cervical spinal cord. Less devastating nerve 2 head injuries caused by cervical traction are phrenic nerve paralysis and Erb or Klumpke palsy, which are caused by brachial plexus stretching or tearing (or both). Shoulder dystocia is commonly associated with clavicular and humeral fractures; femoral shaft fractures occur with breech deliveries. Injuries to the liver, spleen, adrenal glands, and kidneys can cause life-threatening hemorrhage or thrombosis. Vasoocclusion causes tissue loss in the cerebral, coronary, or renal vascular beds. Emergency instrumentation of the airway in the delivery room on rare occasion leads to tracheal and esophageal perforation, particularly in a premature infant.

### Trauma in Children

Accidents and trauma are the leading causes of death in children 1 to 14 years of age.<sup>646</sup> Children are frequently victims of falling or being dropped, drowning, near-drowning, motor vehicle accidents (pedestrian), ingestions, and burns. Head injuries are common, especially in younger children, who have disproportionately large heads and relatively poor neck muscle support.<sup>647</sup> Young children are less likely to be victims of gunshot or knife attacks; blunt injuries are more usual. Blunt trauma to the abdomen can cause solid organ injury (liver and spleen), rather than a perforated viscus. Hypothermia is a frequent complication of trauma; children

lose heat rapidly because they have a relatively large surface-to-volume ratio. Drowning and near-drowning are the prototypical hypothermic injuries. Management of trauma patients of all ages requires an organized approach that permits rapid diagnosis and treatment. Most preventable deaths in pediatric trauma patients are caused by airway obstruction, pneumothorax, and shock; shock is often the result of inadequate treatment of bleeding or secondary brain injury from an expanding intracranial hematoma.<sup>648</sup> The American College of Surgeons recommends a four-step approach to pediatric trauma patients: (1) primary survey, (2) resuscitation, (3) secondary survey, and (4) definitive care.<sup>271</sup> The primary survey requires rapid assessment of the airway, breathing, and circulations. A disproportionately large tongue, in relation to a narrow oropharynx, easily obstructs the airway in an unconscious child. Proper jaw positioning enables bag-and-mask ventilation until the trachea is intubated. Ventilation through an inadequate airway may lead to gaseous distention of the stomach, vomiting, and aspiration of gastric contents. Cervical spine injuries are less common in children than in adults, but the child's neck should be immobilized until spinal injury is excluded. After establishing an airway, adequacy of respiration should be verified by observation of symmetric chest movement, auscultation of normal and equal breath sounds, and an early chest radiograph. Tension hemopneumothorax can be diagnosed clinically and treated by needle aspiration. Aspiration will alleviate the tension and stabilize the patient's condition until a chest tube can be inserted. Circulation can be quickly assessed by looking for tachycardia, poor peripheral perfusion, weak peripheral pulses, and hypotension (which may not occur until blood loss exceeds 25% of the circulating blood volume).<sup>649</sup> A severely hypovolemic child requires rapid insertion of a central venous catheter. If a peripheral venous catheter cannot be inserted expeditiously, an IO cannula should be placed.<sup>650</sup> The amount of volume resuscitation is dictated by the clinical condition of the child and the estimated volume of blood or plasma lost. During the secondary survey, a thorough head-to-toe examination is performed, and a plan of definitive treatment is developed. Diagnostic measures in a pediatric trauma patient are similar to those in adult patients, but there should be consideration of special problems that occur in children. Most intraabdominal injuries requiring laparotomy are recognized clinically because they produce peritonitis or cause increasing abdominal girth.<sup>651</sup> Diagnostic peritoneal lavage may be of help in children who are hemodynamically unstable, despite administering more than 40 mL/kg of blood. Peritoneal lavage may locate the site of occult bleeding in a child too unstable to undergo CT, or it can be used to evaluate abdominal injury in a child about to undergo emergency non-abdominal surgery. Many practitioners forego this procedure if surgery is imminent. Indications for surgical intervention for abdominal trauma include free peritoneal air, evidence of a ruptured viscus, and acute uncontrolled bleeding. A ruptured spleen or a liver laceration is not an indication for surgery in and of itself; the preferred treatment is supportive, blood volume replacement, and reevaluation.<sup>652</sup> A careful head and neurologic examination is done to quickly detect intracranial trauma. The most important indicator of intracranial trauma is a decrease in the level of consciousness. Rapid

diagnosis and treatment of intracranial mass lesions will reduce ICP and may prevent secondary brain injury.

### Child Abuse

The diagnosis of child abuse is made by finding an acute injury that may have a plausible explanation and signs of past trauma, including healing bruises, contusions, and fractures. Child abuse may also take the form of psychological or sexual abuse and failure to meet a child's need for food, clothing, shelter, hygiene, medical care, education, or supervision. Suspicion of child abuse begins with an inappropriate or inadequate explanation for the child's injuries or when the degree of trauma exceeds the stated cause. Multiple hospital admissions, emergency department visits, doctor or hospital "shopping," and a history of previous trauma should be of concern. Frequently, the story regarding the injury changes over time. Certain clinical features are common to child abuse, but they are by no means pathognomonic. Most abused children are older than 3 years and may have poor hygiene and delayed somatic or psychological development. The injuries most commonly include bruises, welts, lacerations, scalds, and burns from cigarettes, stoves, heating grates, or irons. Long-bone fractures, often of varying age, abdominal injuries, signs of smothering, and multiple soft tissue or genital bruises are also common. Head injuries can occur. Shaking an infant can cause neck injuries, intracranial hemorrhage, and contra-coup injuries, without necessarily producing external manifestations of trauma. The approach to a suspected victim of child abuse includes a meticulous and nonjudgmental history, written in detail in the chart. All allegations are recorded and changes in the reported history are documented. The physical examination includes growth parameters, descriptions of soft tissue bruising or burns, and diagrams or preferably photographs of all injuries. The color, shape, placement, and estimated age of all injuries should be catalogued. Laboratory studies should include the following: a skeletal survey of all long bones, ribs, and the skull; a coagulation profile, including hematocrit, platelet count, PT, and PTT; and genital and throat cultures for venereal disease if sexual abuse is suspected. If child abuse is suspected, it must be reported to the authorities.

### Ingestion Injury

Despite the success of various preventive public health programs, poisoning continues to occur commonly in pediatric patients. Fortunately, the vast majority of presumed poisonings in young children can be managed by telephone consultation with a regional poison control center. In one study, acute poisoning accounted for approximately 5% of all medical admissions to a PICU.<sup>653</sup> Approximately half of these admissions were accidental ingestions, and half were attempted suicides. The median age for the accidental poisoning group was 2 years. For the suicide group, it was 15 years. Although many different toxic substances are ingested by children and adolescents, management of poisoning has three main goals: (1) identifying, decontaminating, and eliminating the toxic agents<sup>654</sup>; (2) minimizing the toxic effects on the child; and (3) providing close observation and organ system support until detoxification is complete. Procedures for drug elimination include emesis, gastric lavage, activated charcoal, and magnesium citrate.

Toxic effects can be minimized with specific antidotes when available, by hemodialysis, or by charcoal hemoperfusion. Examples of specific antidotes are deferoxamine for iron ingestion, ethanol infusion for methanol ingestion, naloxone for narcotic overdose, and N-acetylcysteine for acetaminophen ingestion. Because many ingestions, particularly those for attempted suicide, include multiple drugs, specific antidote therapy is only occasionally successful. Organ system support usually includes airway protection and mechanical ventilation, IV fluids, cardiovascular monitoring for arrhythmias and myocardial depression, and anticonvulsive therapy for patients who are seizing. Consultation with clinical pharmacologists or with the regional poison control center and contacting a social worker or psychiatrist are essential aspects of the care of an acutely toxic child. Common complications of ingestions and their therapy include aspiration pneumonia with hydrocarbon ingestion or loss of glottic function, sepsis, respiratory depression, myocardial depression, arrhythmias, seizures, and coma. The psychosocial environment that allowed or precipitated the ingestion must also be considered. Families should be counseled about proper supervision and "child-proofing" their home. Psychiatric intervention should be introduced early; unsuccessful suicide attempts are often repeated.

### Transport of the Critically Ill Child

Transport for critically ill children includes intrahospital and interhospital transport. Intrahospital transport of patients is necessary to and from the operating room. However, this also includes transport for radiologic procedures and studies throughout the hospital. In this circumstance, the clinician who ordered the test must understand the balance of risk and benefit. Is the information that can be obtained by an MRI worth the transport, changes in monitoring, and the time away from the ICU? In the case of a brain MRI, a patient may be away from the unit for 90 to 120 minutes with transport. There are significant differences in the ability to monitor and provide care to those patients. CT scans are certainly shorter but still entail many of the same risks. The severity of the patient's illness must be considered. Any patient with an ETT is at risk for obstruction or dislodgement. Any patient requiring inotropic support is at risk for those medications being interrupted. Depending on the hospital, the team transporting the patient may include a respiratory therapist, bedside nurse, and transport nurse. Some hospitals will send their ICU fellows, and some have a dedicated intrahospital transport team. When new equipment is purchased, transport monitors should be considered that have the ability to monitor end-tidal  $\text{CO}_2$ . In the smallest patients, the maintenance of body temperature can be difficult during transport.

Interhospital transport systems are typically set up by a tertiary care hospital. Smaller community hospitals may use outside resources. One should investigate the capabilities of the transport team available to you. Details to understand include availability of helicopter and fixed wing flight, types of practitioners on the transport team, coverage in the circumstance where the primary team is out on a transport, and the ability to provide interventions when the transport team arrives at the outside facility. Many transport care physicians will be able to intubate, place arterial

and venous lines, and place chest tubes at an outside facility. All of this information is valuable when speaking to the referring hospital. In that regard, the person receiving the transport request may need to make some assessments of whether the patient is safe to transfer by a team that only provides basic life support resuscitation. For hospitals unfamiliar with caring for critically ill children, it may be foremost in their mind to get the child to a higher level of care and out of their hospital. They may not have taken into account what support is available during the transport if the patient deteriorates. They may be unwilling to wait for arrival of a transport team, but the overall needs of the child the focus of the discussion. When deciding on the make-up of the transport team, the distance of the referring hospital, condition of the child, ongoing resuscitation efforts, and chance of change in condition need to be taken into account. While the transport team is en route, the referring hospital should continue to support and resuscitate the child with advice from the receiving hospital. Further information regarding the development of a transport team is beyond the scope of this chapter. One excellent resource is the Guidelines for Air and Ground Transport of Neonatal and Pediatric Patients available through the American Academy of Pediatrics. An understanding of altitude physiology is necessary when considering transport by helicopter. One may not give much thought to the barometric pressure in the alveolar gas equation ( $\text{PAO}_2 = (\text{P}_B - \text{PH}_2\text{O}) (\text{FiO}_2) - (\text{PaCO}_2/\text{R})$ ). This is because at sea level  $\text{P}_B$  is 760 mm Hg. However, at 8000 feet  $\text{P}_B$  is 565 mm Hg. Supplemental oxygen may be needed in flight, and for patients with significant lung disease, low saturation may remain even with supplemental oxygen. From Boyle's law ( $\text{Pressure}_1 \times \text{Volume}_1 = \text{Pressure}_2 \times \text{Volume}_2$ ), there will be expansion of gas with the decreased pressure of altitude. This means that a small pneumothorax can expand to a large pneumothorax. The size of an ETT cuff can expand significantly, putting pressure on the trachea. The pediatric ICU relies significantly on the skills of our transport team. To maintain proficiency, the providers will need to practice intubation and other procedures. Please give some consideration to helping if you are asked to have a transport physician or nurse shadow you in the operating room to get some practice with intubation.

### Acknowledgment

Portions of this chapter are taken from Dr. George Gregory's fine treatment of this topic in the last edition.

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SHERI M. BERG and MATTHIAS R. BRAEHLER

## KEY POINTS

- Emergence from general anesthesia and surgery may be accompanied by a number of physiologic disturbances that affect multiple organ systems. Most common are postoperative nausea and vomiting (PONV), hypoxia, hypothermia and shivering, and cardiovascular instability.
- In a prospective study of more than 18,000 consecutive admissions to the postanesthesia care unit (PACU), the complication rate was found to be as high as 24%. Nausea and vomiting (9.8%), the need for upper airway support (6.8%), and hypotension (2.7%) were the most common problems.
- The most frequent cause of airway obstruction in the immediate postoperative period is the loss of pharyngeal muscle tone in a sedated or obtunded patient. The persistent effects of inhaled and intravenous anesthetics, neuromuscular blocking drugs, and opioids all contribute to the loss of pharyngeal tone in the PACU patient.
- Pharyngeal function is not normalized until an adductor pollicis train-of-four (TOF) ratio is greater than 0.90.
- The ability to strongly oppose the incisor teeth against a tongue depressor is a reliable indicator of pharyngeal muscle tone. This maneuver correlates with an average TOF ratio of 0.85 as opposed to 0.60 for the sustained head lift.
- An estimated 8% to 10% of patients who undergo abdominal surgery subsequently require intubation and mechanical ventilation in the PACU. Respiratory failure in the immediate postoperative period is often due to transient and rapidly reversible conditions such as splinting from pain, diaphragmatic dysfunction, muscular weakness, and pharmacologically depressed respiratory drive.
- Although a combination of leads II and V5 will reflect 80% of the ischemic events detected on a 12-lead ECG, visual interpretation of the cardiac monitor is often inaccurate. Because of human error, the American College of Cardiology guidelines recommend that computerized ST-segment analysis be used (if available) to monitor high-risk patients in the immediate postoperative period.
- In one study, urinary retention was defined as bladder volume greater than 600 mL in conjunction with inability to void within 30 minutes and the incidence of postoperative urinary retention in the PACU was 16%. The most significant predictive factors were age older than 50 years, intraoperative fluid greater than 750 mL, and bladder volume on entry to PACU greater than 270 mL.
- Perioperative attention to adequate hydration is indicated in any patient who has received an intravenous contrast agent. Aggressive hydration with a balanced crystalloid solution provides the single most effective protection against contrast nephropathy.
- Rhabdomyolysis has been reported to occur in 22.7% of 66 consecutive patients undergoing laparoscopic bariatric surgery. Risk factors include increased body mass index (BMI) and duration of operation.
- The incidence of postoperative shivering may be as high as 66% after general anesthesia. Identified risk factors include young age, endoprosthetic surgery, and core hypothermia.
- Multiple studies across different surgical specialties in elective and emergency cases have shown that postoperative delirium is associated with worse surgical outcomes, increased hospital length of stay, functional decline, higher rates of institutionalization, higher mortality, and higher cost and resource utilization.
- PACU Standards of Care require that a physician accept responsibility for the discharge of patients from the unit (Standard V). This is the case even when the decision to discharge the patient is made at the bedside by the PACU nurse in accordance with hospital-sanctioned discharge criteria or scoring systems.

The postanesthesia care unit (PACU) is designed and staffed to monitor and care for patients who are recovering from the immediate physiologic effects of anesthesia and surgery. PACU care spans the transition from one-on-one monitoring in the operating room to the less acute monitoring on the hospital ward or, in some cases, independent function of

the patient at home. To serve this unique transition period, the PACU is equipped to resuscitate unstable patients while providing a tranquil environment for the “recovery” and comfort of stable patients. Its location in close proximity to the operating rooms facilitates rapid access to anesthesiologists for consultation and assistance.

## Admission to the Postanesthesia Care Unit

The PACU is staffed by specially trained nurses skilled in the prompt recognition of postoperative complications. On arrival to the PACU, the anesthesiologist provides the PACU nurse with pertinent details of the patient's history, medical condition, anesthesia, and surgery. Particular attention is directed toward monitoring oxygenation (pulse oximetry), ventilation (breathing frequency, airway patency, capnography), and circulation (systemic blood pressure, heart rate, electrocardiogram [ECG]). Vital signs are recorded as often as necessary but at least every 15 minutes while the patient is in the unit. Vital signs and other pertinent information are recorded as part of the patient's medical record. Specific requirements and recommendations for patient monitoring and therapeutic intervention can be found in the Practice Standards and Guidelines drafted by the American Society of Anesthesiologists.

## The Standards for Postanesthesia Care

Practice Standards delineate the required obligation of minimal care in the clinical setting. As such, they serve as a threshold that can be exceeded when indicated by the clinical judgment of the practitioner. The Standards for Postanesthesia Care are updated on a regular basis to keep up with changing practice parameters and technologic advances. The most recent revision published in 2009 is summarized here<sup>1</sup>:

- I. All patients who have received general anesthesia, regional anesthesia, or monitored anesthesia care shall receive appropriate postanesthesia management.
- II. A patient transported to the PACU shall be accompanied by a member of the anesthesia care team who is knowledgeable about the patient's condition. The patient shall be continually evaluated and treated during transport with monitoring and support appropriate to the patient's condition.
- III. Upon arrival in the PACU, the patient shall be reevaluated and a verbal report provided to the responsible PACU nurse by the member of the anesthesia care team who accompanies the patient.
- IV. The patient's condition shall be evaluated continually in the PACU. The patient shall be observed and monitored by methods appropriate to the patient's medical condition. Particular attention should be given to monitoring oxygenation, ventilation, circulation, level of consciousness, and temperature. During recovery from all anesthetics, a quantitative method of assessing oxygenation such as pulse oximetry shall be employed in the initial phase of recovery.\*
- V. A physician is responsible for the discharge of the patient from the PACU.

\*Under extenuating circumstances, the responsible anesthesiologist may waive the requirements marked with an asterisk (\*): it is recommended that when this is done, it should be stated (including the reasons) in a note in the patient's medical record.

Unlike Practice Standards, Practice Guidelines are not requirements. They are recommendations designed to assist the healthcare provider in clinical decision making. The ASA Practice Guidelines for Post Anesthetic Care are the result of a multiple-step process that incorporates input from three groups: (1) an ASA-appointed task force consisting of private practice and academic anesthesiologists and epidemiologists, (2) PACU consultants, and (3) ASA members at large. The guidelines are based upon literature review, expert opinion, open forum commentary, and clinical feasibility. They recommend the appropriate assessment, monitoring, and treatment of the major organ system functions during recovery from anesthesia and surgery (Box 80.1).<sup>2</sup>

### BOX 80.1 Summary of Recommendations for Patient Assessment and Monitoring in the Postanesthesia Care Unit

#### Respiratory

Assessment of airway patency, respiratory rate, and oxygen saturation should be periodically performed. Particular attention should be given to monitoring oxygenation and ventilation.

#### Cardiovascular

Heart rate and blood pressure should be routinely monitored. Electrocardiographic monitors should be immediately available.

#### Neuromuscular

Assessment of neuromuscular function should be performed for all patients who received nondepolarizing neuromuscular blocking drugs or who have medical conditions associated with neuromuscular dysfunction (also see [Chapter 43](#)).

#### Mental Status

Mental status should be periodically assessed.

#### Temperature

Patient temperature should be periodically assessed.

#### Pain

Pain should be periodically assessed.

#### Nausea and Vomiting

Periodic assessment of postoperative nausea and vomiting should be routinely performed.

#### Hydration

Postoperative hydration should be assessed and managed accordingly. Certain procedures may involve significant blood loss and require additional intravenous fluids management.

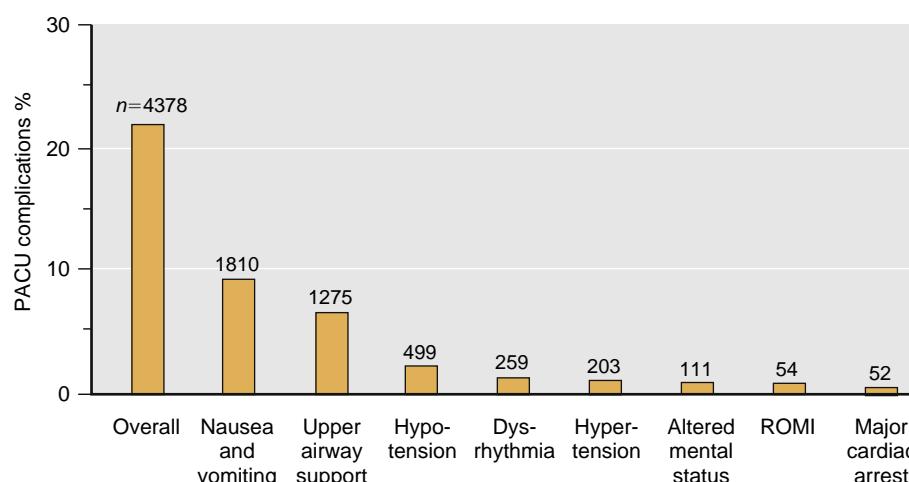
#### Urine

Assessment of urine output and of urinary voiding should be performed on a case-by-case basis for selected patients or selected procedures.

#### Drainage and Bleeding

Assessment of drainage and bleeding should be performed periodically as needed.

From Apfelbaum JL, Silverstein JH, Chung FF, et al. Practice guidelines for postanesthetic care: an updated report by the American Society of Anesthesiologists Task Force on Postanesthetic Care. *Anesthesiology*. 2013;118:291–307.



**Fig. 80.1** The overall complication rate in 18,473 consecutive patients entering a postanesthesia care unit (PACU) was 23.7%. Nausea and vomiting, the need for upper airway support, and hypotension were the most frequent individual complications. (From Hines HR, Barash PG, Watrous G, et al. Complications occurring in the postanesthesia care unit: a survey. *Anesth Analg*. 1992;74:503–509, with permission.)

## Early Postoperative Physiologic Changes

Emergence from general anesthesia and surgery may be accompanied by a number of physiologic disturbances that effect multiple organ systems. Most common are postoperative nausea and vomiting (PONV), hypoxia, hypothermia and shivering, and cardiovascular instability. In a prospective study of more than 18,000 consecutive admissions to the PACU, the complication rate was found to be as high as 24%. Nausea and vomiting (9.8%), the need for upper airway support (6.8%), and hypotension (2.7%) were the most common (Fig. 80.1).<sup>3</sup>

Over a 4-year period ending in 1989, 7.1% of the 1175 anesthesia-related malpractice claims in the United States were attributed to recovery room incidents.<sup>4</sup> Despite the significant incidence of nausea and vomiting in the PACU, serious adverse outcomes correlate more closely with airway/respiratory and cardiovascular compromise. In 2002, airway/respiratory problems (183, 43%) and cardiovascular events (99, 24%) accounted for the majority of 419 recovery room incidents reported to the Australian Incident Monitoring Study database (Table 80.1).<sup>5</sup> Similar data were obtained from the United States closed claims database in 1989, in which critical respiratory incidents accounted for more than one-half of the recovery room malpractice claims.<sup>4</sup>

## Transport to the Postanesthesia Care Unit

Upper airway patency and the effectiveness of the patient's respiratory efforts must be monitored when transporting the patient from the operating room to the PACU. Adequate ventilation can be confirmed by watching for the appropriate rise and fall of the chest wall with inspiration, listening for breath sounds, or simply feeling for exhaled breath with the palm of one's hand over the patient's nose and mouth.

**TABLE 80.1** Primary Presenting Problem in 419 Recovery Room Incidents Reported to Australian Incident Monitoring Study

Primary Presenting Problem	No. (%)
Cardiovascular	99 (24)
Respiratory	97 (23)
Airway	86 (21)
Drug error	44 (11)
Central nervous system	32 (8)
Equipment	27 (6)
Communication problems	7 (2)
Hypothermia	6 (1)
Regional block problems	4 (1)
Inadequate documentation	4 (1)
Hyperthermia	3 (1)
Trauma	3 (1)
Dental problems	2 (0.5)
Renal	1 (0.2)
Skin	1 (0.2)
Blood transfusion	1 (0.2)
Facility limitations	1 (0.2)
Gastrointestinal problems	1 (0.2)

From Kluger MT, Bullock MF. Recovery room incidents: a review of the Anesthetic Incident Monitoring Study (AIMS). *Anesthesia*. 2002;57:1060–1066.

With rare exception, patients who undergo general anesthesia should receive supplemental oxygen during their transport to the PACU. In an observational study of 502 patients admitted to the PACU, breathing room air during transport was the single most significant factor to correlate with hypoxemia ( $\text{SaO}_2 < 90\%$ ) on arrival. Other significant factors included elevated body mass index (BMI), sedation score, and respiratory rate.<sup>6</sup>

Although the majority of otherwise healthy patients undergoing ambulatory surgery can be transported safely breathing room air, the decision to do so must be made on a case-by-case basis. In the ambulatory setting, advanced age ( $>60$  years) and weight ( $>100$  kg) identifies adults who are at increased risk for oxygen desaturation when breathing room air on transport to the PACU.<sup>7</sup> Hypoventilation alone may cause hypoxemia even in healthy patients who undergo minor procedures.

## Upper Airway Obstruction

### LOSS OF PHARYNGEAL MUSCLE TONE

The most frequent cause of airway obstruction in the immediate postoperative period is the loss of pharyngeal muscle tone in a sedated or obtunded patient. The persistent effects of inhaled and intravenous anesthetics, neuromuscular blocking drugs, and opioids all contribute to the loss of pharyngeal tone in the PACU patient.

In an awake patient, opening of the upper airway is facilitated by the contraction of the pharyngeal muscles at the same time that negative inspiratory pressure is generated by the diaphragm. As a result, the tongue and soft palate are pulled forward, tenting the airway open during inspiration. This pharyngeal muscle activity is depressed during sleep, and the resulting decrease in tone can promote airway obstruction. A vicious cycle then ensues wherein the collapse of compliant pharyngeal tissue during inspiration produces a reflex compensatory increase in respiratory effort and negative inspiratory pressure that promotes further airway obstruction.<sup>8</sup>

The effort to breathe against an obstructed airway is characterized by a paradoxical breathing pattern consisting of retraction of the sternal notch and exaggerated abdominal muscle activity. Collapse of the chest wall and protrusion of the abdomen with inspiratory effort produces a rocking motion that becomes more prominent with increasing airway obstruction. Obstruction secondary to loss of pharyngeal tone can be relieved by simply opening the airway with the “jaw thrust maneuver” or continuous positive airway pressure (CPAP) applied via a facemask (or both). Support of the airway is needed until the patient has adequately recovered from the effects of drugs administered during anesthesia. In selected patients, placement of an oral or nasal airway, laryngeal mask airway, or endotracheal tube may be required.

### RESIDUAL NEUROMUSCULAR BLOCKADE

Postoperative residual neuromuscular blockade is unfortunately very common (Box 80.2). The literature reports incidences between 20% and 40%<sup>9</sup> and a recent study even found that 56% of patients had residual neuromuscular blockade upon arrival in the PACU.<sup>10</sup> When evaluating upper airway obstruction in the PACU, the possibility of residual neuromuscular blockade should be considered in any patient who received neuromuscular blocking drugs during anesthesia.<sup>11,12</sup> Residual neuromuscular blockade

### BOX 80.2 Factors Contributing to Prolonged Nondepolarizing Neuromuscular Blockade

#### Drugs

Inhaled anesthetic drugs  
Local anesthetics (lidocaine)  
Cardiac antiarrhythmics (procainamide)  
Antibiotics (polymyxins, aminoglycosides, lincosamines [clindamycin], metronidazole [Flagyl], tetracyclines)  
Corticosteroid agents  
Calcium channel blockers  
Dantrolene

#### Metabolic and Physiologic States

Hypermagnesemia  
Hypocalcemia  
Hypothermia  
Respiratory acidosis  
Hepatic or renal failure  
Myasthenia syndromes  
Excessive dose of succinylcholine  
Reduced plasma cholinesterase activity  
Decreased levels  
■ Extremes of age (newborn, old age)  
■ Disease states (hepatic disease, uremia, malnutrition, plasmaapheresis)  
■ Hormonal changes  
■ Pregnancy  
■ Contraceptives  
■ Glucocorticoids  
Inhibited activity  
■ Irreversible (echothiophate)  
■ Reversible (edrophonium, neostigmine, pyridostigmine)  
Genetic variant (atypical plasma cholinesterase)

may not be evident on arrival in the PACU because the diaphragm recovers from neuromuscular blockade before the pharyngeal muscles do. With an endotracheal tube in place, end-tidal carbon dioxide concentrations and tidal volumes may indicate adequate ventilation while the ability to maintain a patent upper airway and clear upper airway secretions remains compromised. The stimulation associated with tracheal extubation, followed by the activity of patient transfer to the gurney and subsequent encouragement to breathe deeply may keep the airway open during transport to the PACU. Only after the patient is calmly resting in the PACU does upper airway obstruction become evident. Even patients treated with intermediate- and short-acting neuromuscular blocking drugs may manifest residual paralysis in the PACU despite what was deemed clinically adequate pharmacologic reversal in the operating room.

Measurement of the train-of-four (TOF) ratio is a subjective assessment that is often misleading when done by touch or observation alone. A decline in this ratio may not be appreciated until it reaches a value less than 0.4 to 0.5, whereas significant signs and symptoms of clinical weakness persist to a ratio of 0.7.<sup>13</sup> Pharyngeal function is not restored to normal until an adductor pollicis TOF ratio is greater than 0.9.<sup>14</sup>

In the anesthetized patient, a quantitative TOF measurement showing a TOF ratio  $\geq 0.9$  is the most reliable

indicator of adequate reversal of drug-induced neuromuscular blockade.<sup>13,15</sup> Qualitative TOF measurement and 5-second sustained tetanus at 50 Hz are insensitive and will not allow detection of fade above an average TOF ratio of  $0.31 \pm 0.15$ ; 5-second sustained tetanus at 100 Hz is unreliable.<sup>16</sup> In an awake patient, clinical assessment of reversal of neuromuscular blockade is preferred to the application of painful TOF or tetanic stimulation. Clinical evaluation includes grip strength, tongue protrusion, the ability to lift the legs off the bed, and the ability to lift the head off the bed for a full 5 seconds. Of these maneuvers, the 5-second sustained head lift has been considered to be the standard, reflecting not only generalized motor strength but, more importantly, the patient's ability to maintain and protect the airway. However, studies have shown that the 5-second head lift is remarkably insensitive and should not routinely be used to assess recovery from neuromuscular blockade. The ability to strongly oppose the incisor teeth against a tongue depressor is a more reliable indicator of pharyngeal muscle tone. This maneuver correlates with an average TOF ratio of 0.85 as opposed to 0.60 for the sustained head lift.<sup>13</sup> In a year-long study of 7459 PACU patients who had received general anesthesia, Murphy et al. reported critical respiratory events (CREs) in 61 of them. These events occurred within the first 15 minutes of PACU admission, at which time a TOF ratio was measured. When compared with matched controls, these patients had a significantly lower TOF ratio (0.62 [ $+0.20$ ]) compared to controls 0.98 [ $+0.07$ ]).<sup>17</sup> In a recent study, Bulka and associates were able to demonstrate that patients who had received neuromuscular blocking drugs, but did not receive reversal agents, had a 2.26 times higher risk of developing postoperative pneumonia compared to those who did receive reversal agents.<sup>18</sup>

When a PACU patient demonstrates signs and/or symptoms of muscular weakness in the form of respiratory distress and/or agitation, one must suspect that there could be a residual neuromuscular blockade and prompt review of possible etiologic factors is indicated (see **Box 80.2**). Common factors include respiratory acidosis and hypothermia, alone or in combination. Upper airway obstruction as a result of the residual depressant effects of volatile anesthetics or opioids (or both) may result in progressive respiratory acidosis after the patient is admitted to the PACU and external stimulation is minimized. Simple measures such as warming the patient, airway support, and correction of electrolyte abnormalities can facilitate recovery from neuromuscular blockade. The approval of sugammadex in the United States by the FDA in December 2015 may have a major impact on residual paralysis in patients who were paralyzed with aminosteroid neuromuscular blocking drugs (sugammadex does not work with benzylisoquinolinium neuromuscular blocking drugs). While reversal with neostigmine requires a baseline twitch response, and the duration until the patient has a TOF ratio of  $\geq 0.9$  is highly variable, sugammadex can be administered at any depth of neuromuscular blockade and most commonly produces full recovery within several minutes after administration. In a recent study, reversal with sugammadex resulted in a return of TOF ratio to greater than 0.9 within 5 minutes in 85% of patients with no twitches on TOF stimulation.<sup>19</sup> It is anticipated that the increased availability and use of

sugammadex, as an alternative to neostigmine, will result in a decreased incidence of residual neuromuscular blockade in the PACU.

## LARYNGOSPASM

Laryngospasm refers to a sudden spasm of the vocal cords that completely occludes the laryngeal opening via forceful tonic contractions of the laryngeal muscles and descent of the epiglottis over the laryngeal inlet. It typically occurs in the transitional period when the extubated patient is emerging from general anesthesia yet not fully awake. Although laryngospasm is most likely to occur in the operating room at the time of tracheal extubation, patients who arrive in the PACU asleep after general anesthesia are also at risk for laryngospasm upon awakening, which is often triggered by airway irritants, such as secretions or blood. Treatment of laryngospasm involves removal of the stimulus (suctioning of secretions, blood) and the application of a jaw thrust maneuver with CPAP (up to 40 cm water [ $H_2O$ ]) is often sufficient stimulation to break the laryngospasm. However, if jaw thrust maneuver and CPAP fail, then immediate skeletal muscle relaxation can be achieved with succinylcholine (0.1-1.0 mg/kg intravenously [IV] or 4 mg/kg intramuscularly [IM]). If these maneuvers fail, one should proceed with a full dose of an induction agent and intubating dose of a muscle relaxant to enable the practitioner to perform an emergent tracheal intubation; attempting to pass a tracheal tube forcibly through a glottis that is closed because of laryngospasm is not acceptable.

## EDEMA OR HEMATOMA

Airway edema is a possible surgical complication in patients undergoing prolonged procedures in the prone or Trendelenburg position, procedures involving the airway and neck (including thyroidectomy,<sup>20</sup> carotid endarterectomy,<sup>21</sup> and cervical spine procedures<sup>22</sup>), as well as those in which the patient receives a large volume resuscitation. Although facial and scleral edema is an important physical sign that can alert the clinician to the presence of airway edema, visible external signs may not accompany significant edema of pharyngeal tissue (see also **Chapter 44**). Patients who have had a difficult intraoperative intubation and/or airway instrumentation may also have increased airway edema from direct injury. If tracheal extubation is to be attempted in these patients in the PACU, then evaluation of airway patency must precede removal of the endotracheal tube. The patient's ability to breathe around the endotracheal tube can be evaluated by suctioning the oral pharynx and deflating the endotracheal tube cuff. With occlusion of the proximal end of the endotracheal tube, the patient is then asked to breathe around the tube. Good air movement suggests that the patient's airway will remain patent after tracheal extubation. An alternative method involves measuring the intrathoracic pressure required to produce a leak around the endotracheal tube with the cuff deflated. This method was originally used to evaluate pediatric patients with croup before extubation.<sup>23-25</sup> When used in patients with general oropharyngeal edema, the safe pressure threshold can be difficult to identify. Lastly,

when ventilating patients in the volume control mode, one can measure the exhaled tidal volume before and after cuff deflation. Patients who require reintubation generally have a smaller leak (i.e., less percentage difference between exhaled volume before and after cuff deflation) than those who do not. A difference greater than 15.5% is the advocated cutoff value for extubation of the trachea.<sup>26</sup> The presence of a cuff leak demonstrates the likelihood of successful extubation, not a guarantee, just as a failed cuff leak does not rule out a successful extubation.<sup>27</sup> The cuff leak test does not and should never take the place of sound clinical judgment, as it is neither sensitive nor specific; it may be used as an adjunct to aid in providing another layer of guidance.

In order to facilitate the reduction of airway edema, one may sit the patient upright to ensure adequate venous drainage, and consider administering a diuretic and intravenous dexamethasone (4-8 mg every 6 hours for 24 hours), which may help decrease airway swelling.

External airway compression is most often caused by hematomas following thyroid, parathyroid, or carotid surgical procedures. Patients may complain of pain and/or pressure, dysphagia, and can demonstrate signs of respiratory distress as the pressure from the expanding hematoma within the tissue can disrupt both venous and lymphatic drainage, both of which can further exacerbate airway swelling. Mask ventilation may not be possible in a patient with severe upper airway obstruction resulting from edema or hematoma. In the case of a hematoma, an attempt can be made to decompress the airway by releasing the clips or sutures on the wound and evacuating the hematoma. This maneuver is recommended as a temporizing measure, but it will not effectively decompress the airway if a significant amount of fluid or blood (or both) has infiltrated the tissue planes of the pharyngeal wall. If emergency tracheal intubation is required, then ready access to difficult airway equipment and surgical backup to perform an emergency tracheostomy are crucial, as one should assume increased difficulty secondary to laryngeal and airway edema, possible tracheal deviation, and a compressed tracheal lumen. If the patient is able to move adequate air via spontaneous ventilation, then an awake technique is often preferred as visualization of the cords by direct laryngoscopy may not be possible.

## OBSTRUCTIVE SLEEP APNEA

Obstructive sleep apnea (OSA) syndrome is an often overlooked cause of airway obstruction in the PACU, given that most patients are actually not obese and the vast majority of patients are undiagnosed at the time of surgery.<sup>28,29</sup>

It is well known that patients with OSA are at an increased risk of suffering from cardiopulmonary complications as compared to the general population not affected by OSA syndrome. Patients with OSA are particularly prone to airway obstruction and should not be extubated until they are fully awake and following commands.<sup>30,31</sup> Any redundant compliant pharyngeal tissue in these patients not only increases the incidence of airway obstruction, but can also increase the difficulty of intubation by direct laryngoscopy.<sup>32,33</sup> Once in the PACU, a patient with OSA whose trachea has been extubated is exquisitely sensitive to

opioids and, when possible, continuous regional anesthesia techniques should be used to provide postoperative analgesia.<sup>34,35</sup> Other opioid-sparing techniques should be utilized, such as scheduled acetaminophen, and use of nonsteroidal antiinflammatory drugs (NSAIDs) when not contraindicated. One may also employ the use of ketamine, dexmedetomidine, and clonidine, all of which can also decrease postoperative opioid requirements. Interestingly, benzodiazepines can have a greater effect on pharyngeal muscle tone than opioids, and the use of benzodiazepines in the perioperative setting can significantly contribute to airway obstruction in the PACU.<sup>8,36</sup>

Another strategy to employ when caring for a patient with OSA is to position them in either an upright (seated, reverse Trendelenburg) or semi-upright position whenever possible, as the supine position is known to worsen OSA.

In addition, the use of goal-directed fluid strategies should be utilized with consideration of lower salt-containing substances, as these patients are more prone to fluid shifts, which can worsen airway edema.

When caring for a patient with OSA, plans should be made preoperatively to provide CPAP in the immediate postoperative period. Patients should be asked to bring their own CPAP machines with them on the day of surgery to enable the equipment to be set up before the patient's arrival in the PACU. Patients who do not routinely use CPAP at home or who do not have their machines with them may require additional attention from the respiratory therapist to ensure proper fit of the CPAP delivery device (mask or nasal airways) and to determine the amount of positive pressure needed to prevent upper airway obstruction.<sup>37,38</sup>

In patients with OSA who are morbidly obese, immediately applying CPAP postextubation in the operating room rather than waiting to apply positive pressure in the PACU may offer additional benefits. In patients undergoing laparoscopic bariatric surgery, Neligan and colleagues compared the application of 10 cm H<sub>2</sub>O CPAP immediately postextubation to instituting the same CPAP 30 minutes later in the PACU. When compared with matched controls, patients who received immediate CPAP demonstrated improved spirometric lung function (i.e., functional residual capacity [FRC], peak expiratory flow [PEF], and forced expiratory volume [FEV]) at 1 hour and 24 hours postoperatively.<sup>38</sup>

Two large cohort studies demonstrated that patients with OSA who are not treated with positive airway pressure (PAP) preoperatively are at increased risk for cardiopulmonary complications after general and vascular surgery and that PAP therapy was associated with a reduction in postoperative cardiovascular complications. If the patient can tolerate PAP, and their surgical procedure is not a contraindication to its application, patients with OSA should use a PAP device postoperatively.

## Management of Upper Airway Obstruction

An obstructed upper airway requires immediate attention. Efforts to open the airway by noninvasive measures should be attempted before reintubation of the trachea. Jaw thrust

with CPAP (5–15 cm H<sub>2</sub>O) is often enough to tent the upper airway open in patients with decreased pharyngeal muscle tone. If CPAP is not effective, an oral, nasal, or laryngeal mask airway can be inserted rapidly. After successfully opening the upper airway and ensuring adequate ventilation, the cause of the upper airway obstruction should be identified and treated. In adults the sedating effects of opioids and benzodiazepines can be reversed with persistent stimulation or small, titrated doses of naloxone (0.3–0.5 µg/kg IV) or flumazenil (0.2 mg IV to maximum dose of 1 mg), respectively. Residual effects of neuromuscular blocking drugs can be reversed pharmacologically or by correcting contributing factors such as hypothermia.

## Differential Diagnosis of Arterial Hypoxemia in the Postanesthesia Care Unit

Atelectasis and alveolar hypoventilation are the most common causes of transient postoperative arterial hypoxemia in the immediate postoperative period.<sup>39</sup> Clinical correlation should guide the workup of a postoperative patient who remains persistently hypoxic.<sup>40</sup> Review of the patient's history, operative course, and clinical signs and symptoms will direct the workup to rule in possible causes (Box 80.3).

### ALVEOLAR HYPOVENTILATION

Review of the alveolar gas equation demonstrates that hypoventilation alone is sufficient to cause arterial hypoxemia in a patient breathing room air (Fig. 80.2). At sea level, a normocapnic patient breathing room air will have an alveolar oxygen pressure (PAO<sub>2</sub>) of 100 mm Hg. Thus, a healthy patient without a significant alveolar-arterial gradient will have a Pao<sub>2</sub> near 100 mm Hg. In the same patient, an increase in Paco<sub>2</sub> from 40 to 80 mm Hg (alveolar hypoventilation) results in a Pao<sub>2</sub> of 50 mm Hg. Hence, even a patient with normal lungs will become hypoxic if allowed to significantly hypoventilate while breathing room air.

Normally, minute ventilation increases linearly by approximately 2 L/min for every 1-mm Hg increase in Paco<sub>2</sub>. In the immediate postoperative period, the residual effects of inhaled anesthetics, opioids, and sedative-hypnotics can significantly depress this ventilatory response to carbon dioxide. In addition to depressed respiratory drive, the differential diagnosis of postoperative hypoventilation includes generalized weakness due to residual neuromuscular blockade or underlying neuromuscular disease. The presence of restrictive pulmonary conditions, such as preexisting chest wall deformity, postoperative abdominal binding, or abdominal distention, can also contribute to inadequate ventilation.

Arterial hypoxemia secondary to hypercapnia can be reversed by the administration of supplemental oxygen (Fig. 80.3)<sup>41</sup> or by normalizing the patient's Paco<sub>2</sub> by external stimulation of the patient to wakefulness, pharmacologic reversal of opioid or benzodiazepine effect, or controlled mechanical ventilation of the patient's lungs.

### BOX 80.3 Factors Contributing to Postoperative Arterial Hypoxemia

- Right-to-left intrapulmonary shunt (atelectasis)
- Mismatching of ventilation to perfusion (decreased functional residual capacity)
- Congestive heart failure
- Pulmonary edema (fluid overload, postobstructive edema)
- Alveolar hypoventilation (residual effects of anesthetics and/or neuromuscular blocking drugs)
- Diffusion hypoxia (unlikely if receiving supplemental oxygen)
- Inhalation of gastric contents (aspiration)
- Pulmonary embolus
- Pneumothorax
- Increased oxygen consumption (shivering)
- Sepsis
- Transfusion-related lung injury
- Adult respiratory distress syndrome
- Advanced age
- Obesity

$$\text{PAO}_2 = \text{FiO}_2 (\text{PB} - \text{PH}_2\text{O}) - \frac{\text{Paco}_2}{\text{RQ}}$$

$$\text{Paco}_2 = 40 \text{ mm Hg}$$

$$\text{PAO}_2 = 21(760 - 47) - \frac{40}{0.8} = 150 - 50 = 100 \text{ mm Hg}$$

$$\text{Paco}_2 = 80 \text{ mm Hg}$$

$$\text{PAO}_2 = 21(760 - 47) - \frac{80}{0.8} = 150 - 100 = 50 \text{ mm Hg}$$

PAO<sub>2</sub> = alveolar oxygen pressure

Paco<sub>2</sub> = partial pressure of CO<sub>2</sub> in arterial blood

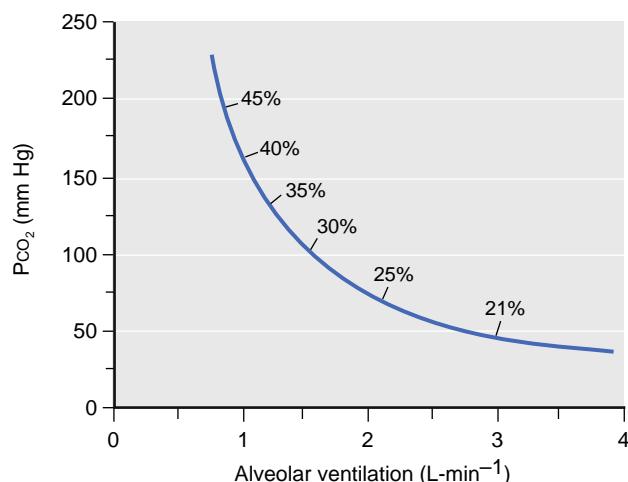
FiO<sub>2</sub> = fraction of inspired oxygen

PB = barometric pressure

PH<sub>2</sub>O = vapor pressure of water

RQ = respiratory quotient

**Fig. 80.2** Hypoventilation as a cause of arterial hypoxemia. (From Nicholau D. Postanesthesia recovery. In: Miller RD, Pardo MC Jr, eds. *Basics of Anesthesia*. 7th ed. Philadelphia: Elsevier; 2018.)



**Fig. 80.3** Alveolar partial pressure of carbon dioxide (Pco<sub>2</sub>) as a function of alveolar ventilation at rest. The percentages indicate the inspired oxygen concentration required to restore alveolar partial pressure of oxygen (Pao<sub>2</sub>) to normal. (Adapted from Nunn JF. *Nunn's Applied Respiratory Physiology*. 6th ed. Philadelphia: Butterworth-Heinemann; 2005, with permission.)

## DECREASED ALVEOLAR OXYGEN PRESSURE

Diffusion hypoxia refers to the rapid diffusion of nitrous oxide into alveoli at the end of a nitrous oxide anesthetic. Nitrous oxide dilutes the alveolar gas and produces a transient decrease in  $\text{PaO}_2$  and  $\text{Paco}_2$ . In a patient breathing room air, the resulting decrease in  $\text{PaO}_2$  can produce arterial hypoxemia while decreased  $\text{Paco}_2$  can depress the respiratory drive. In the absence of supplemental oxygen administration, diffusion hypoxia can persist for 5 to 10 minutes after discontinuation of a nitrous oxide anesthetic; therefore, it may contribute to arterial hypoxemia in the initial moments in the PACU.

## VENTILATION-PERFUSION MISMATCH AND SHUNT

Hypoxic pulmonary vasoconstriction refers to the attempt of normal lungs to optimally match ventilation and perfusion. This response constricts vessels in poorly ventilated regions of the lung and directs pulmonary blood flow to well-ventilated alveoli. In the PACU, the residual effects of inhaled anesthetics and vasodilators such as nitroprusside and dobutamine used to treat systemic hypertension or improve hemodynamics will blunt hypoxic pulmonary vasoconstriction and contribute to arterial hypoxemia.

Unlike a mismatch, a true shunt will not respond to supplemental oxygen. Causes of postoperative pulmonary shunt include atelectasis, pulmonary edema, gastric aspiration, pulmonary emboli, and pneumonia. Of these, atelectasis is probably the most common cause of pulmonary shunting in the immediate postoperative period. Mobilization of the patient to the sitting position, incentive spirometry, and PAP by facemask can be effective in treating atelectasis.

## INCREASED VENOUS ADMIXTURE

Increased venous admixture typically refers to low cardiac output states. It is due to the mixing of desaturated venous blood with oxygenated arterial blood. Normally, only 2% to 5% of cardiac output is shunted through the lungs, and this shunted blood with a normal mixed venous saturation has a minimal effect on  $\text{PaO}_2$ . In low cardiac output states, blood returns to the heart severely desaturated. Additionally, the shunt fraction increases significantly in conditions that impede alveolar oxygenation, such as pulmonary edema and atelectasis. Under these conditions, mixing of desaturated shunted blood with saturated arterialized blood decreases  $\text{PaO}_2$ .

## DECREASED DIFFUSION CAPACITY

A decreased diffusion capacity may reflect the presence of underlying lung disease such as emphysema, interstitial lung disease, pulmonary fibrosis, or primary pulmonary hypertension. In this regard, the differential diagnosis of arterial hypoxemia in the PACU must include the contribution of any preexisting pulmonary condition.

Finally, keep in mind that inadequate oxygen delivery may result from an unrecognized disconnection of the oxygen source or empty oxygen tank.

## Pulmonary Edema

Pulmonary edema in the immediate postoperative period is often cardiogenic in nature, secondary to intravascular volume overload or congestive heart failure. Other causes of noncardiogenic pulmonary edema, namely postobstructive pulmonary edema (secondary to airway obstruction), sepsis, or transfusion (transfusion-related acute lung injury [TRALI]), may occur less frequently, but they must not be overlooked as a potential cause of pulmonary edema in the postoperative period.

## POSTOBSTRUCTIVE PULMONARY EDEMA

Postobstructive pulmonary edema (also referred to as negative pressure pulmonary edema, NPPE) is a rare, but significant consequence of laryngospasm and other upper airway obstruction that may follow tracheal extubation at the conclusion of anesthesia and surgery. Laryngospasm is likely the most common cause of postobstructive pulmonary edema in the PACU, but postobstructive pulmonary edema may result from any condition that occludes the upper airway.<sup>42-45</sup> The etiology of NPPE is multifactorial, but is clearly correlated with the generation of exaggerated negative intrathoracic pressure attributable to forced inspiration against a closed glottis. The resulting negative intrathoracic pressure augments blood flow to the right side of the heart, which in turn dilates and increases hydrostatic pressure gradient across the pulmonary vascular bed, promoting the movement of fluid into the interstitial and alveolar spaces from the pulmonary capillaries. Negative inspiratory pressure will also increase left ventricular afterload, thus decreasing the ejection fraction, which heightens left ventricular end diastolic pressure, left atrial pressure, and pulmonary venous pressure. This chain of events further escalates the development of pulmonary edema via increase of pulmonary hydrostatic pressures. Patients who are muscularly healthy are at increased risk of postobstructive pulmonary edema secondary to their ability to generate significant inspiratory force.

The resulting arterial hypoxemia develops relatively quickly (usually observed within 90 minutes of the upper airway obstruction), and is accompanied by dyspnea, pink frothy sputum, and bilateral fluffy infiltrates on the chest radiograph. Treatment is generally supportive and includes supplemental oxygen, diuresis, and, in severe cases, initiation of positive-pressure ventilation. The general consensus of postoperative monitoring in these patients ranges anywhere from 2 to 12 hours. Resolution of NPPE typically occurs within 12 to 48 hours when recognized and treated immediately; however, if diagnosis and resulting therapy is delayed, mortality rates can reach 40%. Although it is quite uncommon, pulmonary hemorrhage and hemoptysis have been observed.

## TRANSFUSION-RELATED ACUTE LUNG INJURY

The differential diagnosis of pulmonary edema in the PACU should include transfusion-related lung injury in any patient who intraoperatively received blood products.<sup>46-48</sup> Transfusion-related lung injury is typically exhibited within 2 to 4 hours after the transfusion of plasma-containing blood products, including packed red blood cells, whole blood, fresh frozen plasma, or platelets. TRALI occurs when recipient neutrophils become activated by constituents of the donor blood products. These neutrophils then release inflammatory mediators which initiate the cascade of pulmonary edema and resulting lung injury via increasing the permeability of the pulmonary vasculature. Given that presenting symptoms (sudden onset of hypoxic respiratory failure) can appear up to 6 hours after the conclusion of the transfusion, the syndrome may develop during the patient's stay in the PACU. The resulting noncardiogenic pulmonary edema is often associated with fever, pulmonary infiltrates on chest radiograph (without signs of left heart failure), cyanosis, and systemic hypotension. If a complete blood cell count is obtained with the onset of symptoms, then documenting an acute drop in the white blood cell count (leukopenia) is possible, reflecting the sequestration of granulocytes within the lung and exudative fluid.<sup>49,50</sup>

Treatment is supportive and includes supplemental oxygen and diuresis. It is estimated that up to 80% of patients will recover within 48 to 96 hours. Mechanical ventilation may be needed to support hypoxemia and respiratory failure. Vasopressors may be required to treat refractory hypotension.<sup>51,52</sup>

In past years, the lack of specific diagnostic criteria has resulted in the underdiagnosing and underreporting of this syndrome. Recently, a group of transfusion experts in the American-European Consensus Conference developed and implemented diagnostic criteria that have raised the awareness of the syndrome (Box 80.4).<sup>51,53-56</sup>

## TRANSFUSION-ASSOCIATED CIRCULATORY OVERLOAD (TACO)

TACO may be difficult to distinguish from TRALI, however TACO should be highly considered in patients who have diminished cardiac function at baseline, renal insufficiency, and in surgical procedures where there is both rapid and large-volume fluid and blood product administration.<sup>57</sup> Patients with TACO are essentially unable to manage the rate and/or volume of product received secondary to their underlying comorbidities, and tend to develop symptoms of respiratory distress, hypoxemia, and signs of left and/or right heart failure within 2 to 6 hours of the transfusion. TACO is commonly associated with physical manifestations of fluid overload and these patients frequently are hypertensive during the onset of dyspnea. The chest radiograph may demonstrate findings of preexisting cardiac disease and a possible cardiogenic component, such as cardiomegaly and pleural effusions. Elevated levels of BNP are suggestive of TACO. TACO and TRALI may indeed coexist. Treatment is mainly supportive and should focus on treatment of supplemental oxygen for hypoxemia and diuresis for acute volume overload. Positive pressure ventilation can be employed as well.

### BOX 80.4 Criteria for the Diagnosis of Transfusion-Related Acute Lung Injury: the American-European Consensus Conference Recommendations

1. Acute lung injury evidenced by:
  - a. Acute onset of signs and symptoms
  - b. Hypoxemia:
    - i.  $\text{PaO}_2/\text{FiO}_2 < 300$ , or
    - ii. Room air  $\text{SpO}_2 < 90\%$ , or
    - iii. Other clinical evidence of hypoxemia
  - c. Bilateral infiltrates on chest radiography without cardiomegaly
  - d. No clinical evidence of left atrial hypertension
2. No preexisting acute lung injury before transfusion
3. Onset of lung dysfunction within 6 h of transfusion
4. No temporal association of onset to alternative causes of acute lung injury

$\text{FiO}_2$ , Fraction of inspired oxygen;  $\text{PaO}_2$ , Arterial oxygen pressure;  $\text{SpO}_2$ , oxygen saturation by pulse oximetry.

Modified from Swanson K, Dwyre DM, Krochmal J, et al. Transfusion-related acute lung injury (TRALI): current clinical and pathophysiologic considerations. *Lung*. 2006;184:177-185.

## Monitoring and Treatment of Hypoxemia

### OXYGEN SUPPLEMENTATION

In the era of cost containment, it has been suggested that the routine delivery of supplemental oxygen to all patients recovering from general anesthesia is a costly and unnecessary practice.<sup>58</sup> The argument against the use of routine oxygen supplementation relies on the fact that continuous pulse oximetry, now a PACU standard, readily identifies those patients who will require oxygen therapy.<sup>59</sup> Supporting this argument is the observation that after general anesthesia a majority of patients do not become hypoxic (63% at threshold of  $\text{Sao}_2 < 90\%$ , and 83% at threshold of  $\text{Sao}_2 < 94\%$ ) when breathing room air in the PACU.<sup>59</sup> Although the authors of this observational study predict that the elimination of routine oxygen supplementation in the PACU would result in significant cost savings, others assert that the economic benefit of limited oxygen therapy is likely to be offset by the cost of complications.<sup>60,61</sup>

Although the practice of providing prophylactic oxygen therapy to all patients after general anesthesia is controversial, most would argue that the benefits outweigh the risks. Even with oxygen supplementation, a significant percentage of patients will become hypoxic at some point during their PACU stay.<sup>62,63</sup> Russell and associates studied 100 patients who were transferred to the PACU breathing room air before receiving at least 40% oxygen by aerosol face tent in the unit.<sup>62</sup> All patients had an  $\text{Sao}_2$  greater than 97% before the 2-minute transport to the PACU. Fifteen percent of patients experienced transient desaturation on arrival in the PACU (<92% saturation for >30 seconds). This immediate desaturation correlated positively with patient age, body weight, ASA classification, general anesthesia, and increased volume of

intravenous fluid greater than 1500 mL. An even larger percentage of patients (25%) desaturated 30 to 50 minutes later in their PACU stay despite prophylactic oxygen administration. These later desaturations were more severe (71%-91%) and lasted longer ( $5.8 \pm 12.6$  minutes) than those that occurred on admission. Additional correlating factors included duration of anesthesia and female gender.

The safe practice of postanesthesia care without oxygen supplementation requires ideal conditions at all times; that is, functioning oxygen delivery apparatus at every bedside as well as sufficient manpower for observation and immediate intervention. Gravenstein argues that this degree of vigilance is likely unrealistic and the risk of adverse outcome to even a small number of patients is unwarranted.<sup>64</sup>

### LIMITATIONS OF PULSE OXIMETRY

The ASA Standards for Postanesthesia Care require that patients be observed and monitored with “particular attention given to” both oxygenation and ventilation. The pulse oximeter is a standard monitor in the PACU for the detection of hypoxemia, but it does not reflect the adequacy of ventilation.<sup>65</sup> Although several studies have demonstrated oximetry’s limited ability to detect hypoventilation in patients breathing room air,<sup>66,67</sup> they confirm that it does not reliably detect hypoventilation in patients breathing oxygen.<sup>67</sup> When monitoring ventilation in the PACU, pulse oximetry is not a substitute for close observation by trained personnel.

## Oxygen Delivery Systems

### SUPPLEMENTAL OXYGEN

The degree of hypoxemia, the surgical procedure, and patient compliance determine the oxygen delivery system of choice in the PACU. Regardless of the delivery system, oxygen should be humidified in order to prevent the subsequent dehydration of the nasal and/or oral mucosa. Patients who have just undergone head and neck surgery may not be candidates for facemask oxygen because of the risk of pressure necrosis on incision sites and microvascular muscle flaps, whereas nasal packing prohibits the use of nasal cannulas in others. Face tent oxygen or blow-by setups are viable alternatives in cases in which tight-fitting masks and straps are contraindicated. In an elderly patient, or one who is at an increased risk of delirium, nasal cannula may be selected over a facemask, as long as their oxygenation saturation levels are adequate.

Simple facemasks are generally used in the postoperative setting in patients who are breathing spontaneously yet require a higher oxygen flow rate and/or concentration in order for them to maintain their oxygenation saturation. The practitioner should ensure the proper size, as the mask should fit comfortably over the patient’s nose and mouth. Oxygen flow rates should be at least 5 L/min in order to preclude rebreathing of CO<sub>2</sub>. Nonrebreather masks have traditionally been known to deliver

the highest concentration (up to 95%) in spontaneously breathing patients.

The delivery of oxygen through a traditional nasal cannula with bubble humidifier is usually limited to a maximum flow of 6 L/min to minimize the discomfort and complications that result from inadequate humidification. As a general rule, each liter per minute of oxygen flow through nasal cannula increases the FiO<sub>2</sub> by 0.04, with 6 L/min delivering an FiO<sub>2</sub> of approximately 0.44.

Until recently, maximum oxygen delivery to extubated patients required delivery by facemask through a nonrebreather system or high-flow nebulizer. These systems can be inefficient, however, because of inadequate mask fit and/or high-minute ventilation requirements that result in significant entrainment of room air. The newer high-flow nasal cannula (HFNC) devices can comfortably deliver oxygen at 40 L/min, 37°C, and 99.9% relative humidity.<sup>68</sup> The delivery of high-flow oxygen directly to the nasopharynx produces an FiO<sub>2</sub> equal to that delivered by traditional mask devices. HFNC is an appropriate alternative in patients with hypoxic respiratory failure without hypercapnia. In fact, the Vapotherm system has been shown to deliver a higher FiO<sub>2</sub> than a nonrebreather mask at similar flow ranges (10-40 L/min). Unlike the nonrebreather mask, these devices deliver high-flow oxygen directly to the nasopharynx throughout the respiratory cycle.<sup>69,70</sup> The efficacy of these devices may be enhanced by a CPAP effect resulting from the high gas flow.<sup>71</sup>

In a recent meta-analysis by Zhao et al., it was concluded that HFNC, when compared to conventional oxygen therapy systems, reduced the need for mechanical ventilation<sup>72</sup>; however outcomes were similar when compared to noninvasive ventilation.

### CONTINUOUS POSITIVE AIRWAY PRESSURE

An estimated 8% to 10% of patients who undergo abdominal surgery subsequently require intubation and mechanical ventilation in the PACU. As discussed earlier in this chapter, respiratory failure in the immediate postoperative period is often due to transient and rapidly reversible conditions such as splinting from pain, diaphragmatic dysfunction, muscular weakness, and pharmacologically depressed respiratory drive. Readily reversible hypoxemia may be due to hypoventilation, atelectasis, or volume overload. The application of CPAP in this setting can potentially decrease hypoxemia as a result of atelectasis by recruiting alveoli. The resulting increase in functional reserve capacity may also improve pulmonary compliance and decrease the work of breathing.

A large percentage of patients who are obese and undergoing Roux-en-Y gastric bypass surgery have OSA and stand to benefit significantly from postoperative CPAP therapy. Yet surgeons were initially hesitant to embrace this modality for fear that applying positive pressure to the airway would inflate the stomach and proximal intestine and result in anastomotic disruption. In a single-center study of 1067 patients undergoing gastro-jejunostomy bypass and 420 diagnosed with OSA, CPAP did not increase the risk of postoperative anastomotic leaks.<sup>73</sup>

## NONINVASIVE POSITIVE-PRESSURE VENTILATION

Even with the application of CPAP in the PACU, a number of patients will require additional ventilatory support. Noninvasive positive-pressure ventilation (NIPPV) has been shown to be an effective alternative to endotracheal intubation in the intensive care unit (ICU) setting. Although the use of NIPPV in both chronic and acute respiratory failure is well established, its application in the PACU is limited.

In the past, the use of NIPPV was avoided in the immediate postoperative period because of the potential for gastric distention, aspiration, and wound dehiscence. These potential complications were especially true in patients who had undergone esophageal or gastric surgery. Careful consideration of both the patient and the surgical factors must guide the decision to use noninvasive modes of ventilation in the PACU. Relative contraindications include hemodynamic instability or life-threatening arrhythmias, altered mental status, high risk of aspiration, inability to use nasal or facial mask (head and neck procedures), and refractory hypoxemia.<sup>74,75</sup>

NIPPV can be delivered by facemask using the pressure support mode of a mechanical ventilator. Alternatively, the use of a biphasic PAP machine allows the delivery of positive pressure by either nasal cannula or facemask. An example protocol for instituting NIPPV in patients with acute respiratory failure is shown in *Box 80.5*.<sup>76</sup>

NIPPV should be considered postoperatively in patients with OSA, COPD, and cardiogenic pulmonary edema. Utilization of PPV postextubation in the immediate postoperative periods may aid in the prevention of atelectasis as well as ensuing respiratory failure. There have been several studies that investigated the prophylactic use of NIPPV in the bariatric, general, thoracic, and vascular surgical populations. Despite the fact that there is lack of data demonstrating succinct results and large RCTs, NIPPV has shown to be beneficial in distinctive patient populations.<sup>77</sup>

Patients who are able to cooperate and tolerate PPV, as well as those with an intact mental status, moderate hypercarbia and academia ( $\text{PaCO}_2$  45-92, pH 7.1-7.35), and physiologic improvement within 2 hours are often associated with higher rates of success with NIPPV. Relative contraindications to PPV include copious secretions, lack of an intact mental status, cardiac or respiratory arrest, and those who are considered to be high aspiration risks or are unable to protect their airway.

## Hemodynamic Instability

Hemodynamic compromise in the patient in the PACU is exhibited in a number of ways—systemic hypertension, hypotension, tachycardia, or bradycardia—alone or in combination. Hemodynamic instability in the PACU has a negative impact on long-term outcome. Interestingly, postoperative systemic hypertension and tachycardia are associated with an increased risk of unplanned critical care admission and a higher mortality than hypotension and bradycardia.<sup>78</sup>

### BOX 80.5 Example Protocol for Instituting Noninvasive Positive-Pressure Ventilation in Patients with Acute Respiratory Failure

1. Choose the appropriate patient, based on the surgical procedure and the patient's risk of aspiration, ability to protect his or her airway, and ability to comply with the mask fit.
2. Position the head of the bed at  $\geq 45$ -degree angle.
3. Choose the correct size mask and connect mask to ventilator.
4. Explain the modality to the patient and provide reassurance.
5. Set initial ventilatory settings (CPAP, 0 cm  $\text{H}_2\text{O}$ ; pressure support, 10 cm  $\text{H}_2\text{O}$ ).
6. Gently hold mask on face until the patient is comfortable and synchronous with ventilation.
7. Apply wound care dressing on nasal bridge and other pressure points.
8. Secure mask with head straps.
9. Slowly increase CPAP.
10. Adjust pressure support to achieve adequate tidal volumes and maximal patient comfort.
11. In patients with hypoxia, increase CPAP in increments of 2 to 3 cm  $\text{H}_2\text{O}$  until  $\text{FiO}_2$  is  $\leq 0.6$ .
12. Avoid peak mask pressures  $>30$  cm  $\text{H}_2\text{O}$ .
13. Set ventilator alarms and apnea backup parameters.
14. Ask the patient and nurse to call for needs (e.g., repositioning mask, pain, discomfort) or if complications occur (e.g., respiratory difficulties, abdominal distention, nausea, vomiting).
15. Monitor with oximetry, and adjust ventilator settings after blood gas results.

CPAP, Continuous positive airway pressure;  $\text{FiO}_2$ , fraction of inspired oxygen.

Modified from Abou-Shala N, Meduri U. Noninvasive mechanical ventilation in patients with acute respiratory failure. *Crit Care Med*. 1996;24:705-715.

## SYSTEMIC HYPERTENSION

Patients with a history of essential hypertension are at greatest risk for significant systemic hypertension in the PACU, especially if they did not take their morning anti-hypertensive medications.<sup>79</sup> Additional factors include pain (which is usually associated with tachycardia +/- tachypnea), nausea and vomiting, hypoventilation and associated hypercapnia, hypoxia, emergence excitement, anxiety, agitation, advanced age, urinary retention (secondary to large intraoperative administration of IV fluids), and preexisting renal disease (*Box 80.6*). One must also not forget the possibility of alcohol withdrawal (which can occur as early as 24 hours after the patient's last alcohol consumption). Drug withdrawal must also be considered as a possibility; this can be secondary to  $\beta$ -blocker withdrawal, or opioid or benzodiazepine withdrawal as well. Recent use/abuse of certain recreational drugs, such as cocaine, methamphetamines, or LSD/PCP can all produce exaggerated sympathetic states and patients under the influence of these will present with tachycardia and hypertension.

The surgical procedures most commonly associated with postoperative hypertension are carotid endarterectomy and intracranial procedures. A significant number of patients, especially those with a known history of hypertension, will require pharmacologic blood pressure control in the PACU.

### BOX 80.6 Factors Leading to Postoperative Hypertension

- Preoperative hypertension
- Arterial hypoxemia
- Hypervolemia
- Emergence excitement
- Shivering
- Drug rebound
- Increased intracranial pressure
- Increased sympathetic nervous system activity
  - Hypercapnia
  - Pain
  - Agitation
  - Bowel distention
  - Urinary retention

### BOX 80.7 Differential Diagnosis of Hypotension in the Postanesthesia Care Unit

- Intravascular volume depletion
  - Persistent fluid losses
  - Ongoing third-space translocation of fluid
  - Bowel preparation
  - Gastrointestinal losses
  - Surgical bleeding
- Increased capillary permeability
  - Sepsis
  - Burns
  - Transfusion-related acute lung injury
- Decreased cardiac output
  - Myocardial ischemia or infarction
  - Cardiomyopathy
  - Valvular disease
  - Pericardial disease
  - Cardiac tamponade
  - Cardiac dysrhythmias
  - Pulmonary embolus
  - Tension pneumothorax
  - Drug induced ( $\beta$ -blockers, calcium channel blockers)
- Decreased vascular tone
  - Sepsis
  - Allergic reactions (anaphylactic, anaphylactoid)
  - Spinal shock (cord injury, iatrogenic high spinal)
  - Adrenal insufficiency

## SYSTEMIC HYPOTENSION

Postoperative systemic hypotension may be characterized as (1) hypovolemic (decreased preload), (2) distributive (decreased afterload), (3) cardiogenic (intrinsic pump failure), and/or (4) extracardiac/obstructive. (Box 80.7).

Regardless of the type of shock the patient is in postoperatively, the underlying cause must be identified and treated. Fluids, blood products, and vasopressors can be used as needed to restore intravascular volume and support adequate perfusion while the patient is being assessed or undergoing a subsequent therapeutic procedure.

### Hypovolemic (Decreased Preload)

Systemic hypotension in the PACU is often due to decreased intravascular fluid volume and preload, and, as such, it responds favorably to intravenous fluid administration. Common causes of decreased intravascular fluid volume in the immediate postoperative period include ongoing third-space translocation or loss of fluid, inadequate intraoperative fluid replacement (especially in patients who undergo major intraabdominal procedures or preoperative bowel preparation), and loss of sympathetic nervous system tone as a result of neuraxial (spinal or epidural) blockade.

Patients who are in hypovolemic shock often have typical associated clinical characteristics including tachycardia, tachypnea, hypotension, mottled skin (cool, clammy), venous collapse, decreased urine output, and altered mental status. The amount of volume loss tends to dictate clinical signs, as patients seem to be able to tolerate up to a 10% blood volume loss, with tachycardia being the only sign, whereas when patients lose around 40% of their total blood volume, clear signs of shock are evident (lactic acidosis, severe hypotension, reduced cardiac output).

Ongoing bleeding (hemorrhagic shock) should be ruled out in patients with hypotension who have undergone a surgical procedure in which significant blood loss was possible. Regardless of the estimated intraoperative blood loss, the measured blood loss may be inaccurate. If the patient is unstable, then hemoglobin can be measured at the bedside to eliminate laboratory turnover time. In addition, tachycardia may not be a reliable indicator of hypovolemia or anemia (or both) if the patient is taking  $\beta$ -blockers or calcium channel blockers. Non-hemorrhagic hypovolemia leading to hypotension can be a result of skin losses, especially in burn patients, and ascites, as in patients with liver failure or certain cancers (i.e., ovarian), GI fluid losses, secondary to vomiting and/or diarrhea and should be repleted with appropriate fluids as needed.

The potential for local anesthetic toxicity must be considered when assessing perioperative hypotension. Local anesthetics can become systemic secondary to accidental intravascular injection or following an overdose of injected medication  $+$  rapid absorption. Central nervous system signs, including tinnitus, confusion, altered mental status, and ultimately seizures may not always precede cardiovascular collapse. Once recognized, benzodiazepines should be given to abate seizures and supportive therapy should be instituted immediately to support cardiovascular function. Lipid emulsion therapy (20%) should be initiated, starting with a bolus of 1.5 mL/kg IV over 1 minute followed by a continuous rate of 0.25 mL/kg per minute for 30 minutes. Repeated boluses can be given every 5 minutes if cardiovascular collapse continues.

### Distributive (Decreased Afterload)

Distributive shock in the PACU may be the result of a number of physiologic derangements, including iatrogenic sympathectomy, critical illness, allergic reactions, and sepsis. Iatrogenic sympathectomy, secondary to regional anesthetic techniques, is an important cause of hypotension in the perioperative period. A high sympathetic block (to T4) will decrease vascular tone and block the cardio-accelerator fibers. If not treated promptly, then the resulting

bradycardia in the presence of severe hypotension can lead to cardiac arrest even in young healthy patients.<sup>80</sup> Vasopressors, including phenylephrine and ephedrine, are pharmacologic treatments of hypotension caused by residual sympathetic nervous system blockade.

Patients who are critically ill may rely on exaggerated sympathetic nervous system tone to maintain systemic blood pressure and heart rate. In these patients, even minimal doses of inhaled anesthetics, opioids, or sedative-hypnotics can decrease sympathetic nervous system tone and produce significant systemic hypotension.

Allergic (anaphylactic or anaphylactoid) reactions may be the cause of hypotension in the PACU. In addition to the sometimes-profound hypotension, patients experiencing an allergic reaction/anaphylaxis often present with an associated rash/hives, bronchospasm/wheezing, stridor, and facial edema. Patients should be treated immediately, with prompt removal of the offending agent if known and still present, steroids (hydrocortisone or methylprednisolone), H1 and H2 blockers, fluids, and vasopressors. Epinephrine is the drug of choice to treat hypotension secondary to an allergic reaction. Increased serum tryptase concentrations confirm the occurrence of an allergic reaction, but an elevated tryptase level does not differentiate anaphylactic from anaphylactoid reactions. The blood specimen for tryptase determination must be obtained within 30 to 120 minutes after the allergic reaction, but the results may not be available for several days. Neuromuscular blocking drugs are the most common cause of anaphylactic reactions in the surgical setting followed by latex, antibiotics, and other rare substances (Table 80.2).<sup>81-83</sup>

If sepsis is suspected as the cause of hypotension in the PACU, then blood should be obtained for culture, and empiric antibiotic therapy should be initiated as soon as possible. Urinary tract manipulation and biliary tract procedures are examples of interventions that can result in a sudden onset of severe systemic hypotension secondary to sepsis. Although fluid resuscitation is the most important immediate intervention, pressor support is often required—at least transiently. Norepinephrine is the pressor of choice

in septic patients. Vasopressin deficiency has been shown to contribute to vasodilation in septic shock,<sup>84</sup> and low-dose vasopressin (0.01-0.05 unit/min) improves mean arterial pressure, decreases catecholamine vasopressor requirement, and may spare renal function in severe septic shock.<sup>85</sup>

### Cardiogenic (Intrinsic Pump Failure)

Significant cardiogenic causes of postoperative hypotension include myocardial ischemia and infarction, cardiomyopathy, cardiac tamponade, and cardiac arrhythmias. The differential diagnosis depends on the surgical procedure and the patient's preoperative cardiac risk and medical condition. To determine the cause of the hypotension, central venous pressure monitoring, echocardiography, and, rarely, pulmonary artery catheter monitoring may be required.

Patients can have a similar clinical appearance to those in hypovolemic shock; however one of the cardinal signs here is indication of relative fluid overload/congestive heart failure, such as distended central and peripheral veins, evidence of pulmonary edema, and a possible S3 heart sound on exam. These patients have elevated filling pressures in conjunction with reduced/impaired cardiac output. Cardiogenic shock can ensue when greater than 40% of the myocardium is damaged. Patients with underlying ischemic heart disease, especially if they are undergoing an emergent or high-risk procedure, are notably at increased risk of experiencing an adverse cardiac event. It should also be noted that the mortality rate for those in cardiogenic shock is remarkably high, reaching up to 70%. Patients may require immediate postoperative placement of an intra-aortic balloon pump (IABP), cardiac catheterization and stenting, echocardiography, or a surgical procedure for a mechanical/valvular abnormality.

### Extracardiac/Obstructive Shock

Impairment in diastolic filling which ultimately results in decreased preload can lead to shock if not promptly recognized and treated. IVC compression (vena cava obstruction, intrathoracic tumors), tension pneumothorax, cardiac tamponade, constrictive pericarditis, and even PEEP/mechanical ventilation, can lead to diminished filling and compromise venous return. Intrathoracic tumors and tension pneumothoraces typically have similar clinical presentations to those in hypovolemic shock secondary to obstruction of the great veins, namely tachycardia and hypotension, possibly with associated distended neck veins. Patients in tamponade are also tachycardic and hypotensive; if they have indwelling invasive monitors, one typically can observe the “equalization of pressures” (increased and relatively equal LV and RV diastolic pressures, PAOP, CVP).

Acute pulmonary hypertension, pulmonary embolism, and aortic dissections result in impaired systolic contraction of the left and/or right ventricle secondary to increased afterload. These patients can present in either LV or RV failure, or even both.

Patients may need to undergo emergent needle thoracostomy and chest tube placement for a tension pneumothorax, a pericardiocentesis for tamponade, or thrombolysis/embolectomy for a pulmonary embolism.

**TABLE 80.2** Drugs Involved in Perioperative Anaphylaxis

Substance	Incidence of Perioperative Anaphylaxis (%)	Most Commonly Associated With Perioperative Anaphylaxis
Muscle relaxants	69.2	Succinylcholine, rocuronium, atracurium
Natural rubber latex	12.1	Latex gloves, tourniquets, Foley catheters
Antibiotics	8	Penicillin and other $\beta$ -lactams
Hypnotics	3.7	Propofol, thiopental
Colloids	2.7	Dextran, gelatin
Opioids	1.4	Morphine, meperidine
Other substances	2.9	Propacetamol, aprotinin, chymopapain, protamine, bupivacaine

From Hepner DL, Castells MC. Anaphylaxis during the perioperative period. *Anesth Analg*. 2003;97:1381-1395.

## Myocardial Ischemia: Evaluation and Treatment

Over 1 million people die every year after noncardiac surgery, with myocardial infarction being the most common cardiovascular complication.<sup>86</sup> The incidence of major adverse cardiac events depends on the number of inherent patient risk factors. According to the Revised Goldman Cardiac Risk Index, the risk of an adverse cardiac event can be as high as 5.4% after noncardiac surgery in patients who possess three or more risk factors.<sup>87</sup> Myocardial ischemia is rarely accompanied by chest pain in the recovery room secondary to the fact that patients are still emerging from anesthesia in the immediate postoperative period and are also still under the influence of residual medication effects, especially analgesics. In a study by Mangano et al., 94% of postoperative ischemic episodes were silent.<sup>88</sup>

### EVALUATION

Patients who complain of chest pain in the recovery room should have a 12-lead ECG performed and a troponin level drawn. A physical exam and further workup, as indicated, should be done in order to rule out other causes for chest pain (e.g., pulmonary embolus, aortic dissection, tension pneumothorax, cardiac tamponade, esophageal rupture, etc.). ECG changes, such as ST-segment changes, may not necessarily represent myocardial ischemia (especially in younger patients with no known cardiac disease and no cardiac risk factors), however, should associated signs and symptoms point toward cardiac ischemia, further workup is certainly warranted.

Presently, myocardial ischemia after non-cardiac surgery (MINS) has been established as an entity in itself. MINS is defined as elevated postoperative troponin levels without any clinical symptoms or any changes in the ECG, provided there is no other nonischemic cause for the elevated troponin level (e.g., chronic troponin elevation, pulmonary embolism, sepsis, rapid atrial fibrillation). Elevated troponin levels are independently associated with poor outcomes.<sup>89</sup> An international prospective cohort study found that postoperative elevated troponin after noncardiac surgery was a strong independent predictor of 30-day mortality.<sup>90</sup>

The most recent guidelines established by the American Heart Association/American College of Cardiology (AHA/ACC) recommend obtaining a troponin level for all patients who present with ECG changes suggestive of ischemia or exhibit typical ischemic chest pain after surgery. Furthermore, they recommend drawing serial troponin levels for stable patients after vascular or intermediate risk surgery.<sup>91</sup> A recent multicenter study investigated the association between postoperative high-sensitivity troponin (hsTnT) levels with myocardial injury and 30-day mortality after noncardiac surgery.<sup>92</sup> The authors confirmed that postoperative myocardial injury is most commonly silent, as 93% of patients with MINS did not experience any symptoms. Furthermore, they found that elevated hsTnT levels without an ischemic feature in the first 3 days after noncardiac surgery were associated with a significantly increased

30-day mortality. These newer studies may even warrant a more liberal approach to drawing postoperative hsTnT levels in the PACU.

### TREATMENT

Once the diagnosis of myocardial ischemia/injury has been made, the primary surgical team should immediately be notified and a cardiology consult should be obtained.

After ruling out other life-threatening causes, the patients should receive oxygen, and blood pressure and heart rate should be controlled. If there are no absolute contraindications to their administration, the patient should be given nitroglycerin, a  $\beta$  blocker, a statin, and aspirin. Pain and anxiety should be treated with an opioid and a benzodiazepine, and anemia should be corrected, if present. One should be prepared for further decompensation of the patient and have a code cart readily available. Should the patient become hemodynamically unstable, echocardiography may help in guiding next steps (e.g., placing an IABP, emergent interventions).

Depending on the acuity of the situation, further interventions like fibrinolysis, percutaneous coronary intervention (PCI), or revascularization should be considered and discussed. However, since these patients just had surgery, there are conflicting goals in terms of postoperative bleeding versus coronary blood flow. A mutual approach between surgeon, cardiologist, anesthesiologist, and patient should be chosen to determine the best course of action.

## Cardiac Arrhythmias

Postoperative cardiac arrhythmias are frequently transient and multifactorial. Reversible causes of cardiac arrhythmias in the perioperative period include hypoxemia, hypoventilation and associated hypercapnia, endogenous or exogenous catecholamines, electrolyte abnormalities, acidemia, fluid overload, anemia, and substance withdrawal.<sup>93</sup>

### TACHYCARDIA

Common causes of tachycardia in the PACU include pain, agitation, hypoventilation with associated hypoxia and hypercapnia, hypovolemia, PONV, and shivering. Less common but serious causes include hemorrhage; cardiogenic, septic, or anaphylactic shock; pulmonary embolism; pneumothorax; thyroid storm; and malignant hyperthermia.

When evaluating postoperative tachycardia, the most important question is whether or not the patient is hemodynamically stable. If the patient is stable, oxygen should be administered, a 12-lead ECG obtained, and the underlying rhythm determined. Unstable patients typically present with a heart rate greater than 150 bpm, are hypotensive, and may exhibit other signs of decreased perfusion, for example, altered mental status, chest pain, or shock. These patients should undergo immediate synchronized cardioversion. There are various different causes of tachyarrhythmia in the PACU which warrant individualized approaches regarding the medications to administer and the energy

doses to use for cardioversion. A comprehensive overview can be found in the American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care 2015.<sup>94</sup>

## BRADYCARDIA

Bradycardia in the PACU is often iatrogenic. Drug-related causes include  $\beta$ -blocker therapy, anticholinesterase reversal of neuromuscular blockade, opioid administration, and treatment with clonidine or dexmedetomidine. Procedure- and patient-related causes include bowel distention, increased intracranial or intraocular pressure, hypoxia, hypothermia, hypothyroidism, and spinal anesthesia. A high spinal block can impede the cardioaccelerator fibers originating from T1 through T4, resulting in severe bradycardia. The ensuing sympathectomy and possible intravascular fluid volume depletion along with decreased venous return can produce sudden bradycardia and cardiac arrest, even in young healthy patients.

When evaluating postoperative bradycardia, vital signs and hemodynamic stability should be immediately assessed. Underlying causes should be corrected, if possible. Asymptomatic bradycardia may not need to be treated at all, however, if the patient is unstable and hypotensive, or shows signs of shock, altered mental status, ischemic chest discomfort, or acute heart failure, urgent intervention is indicated. According to the ACLS guidelines, first-line treatment is atropine IV. If this is ineffective, transcutaneous pacing or initiation of a vasopressor (dopamine, epinephrine infusion) is indicated. Eventually, expert consultation and transvenous pacing should be considered.<sup>94</sup>

## ATRIAL ARRHYTHMIAS

The most common atrial arrhythmia is atrial fibrillation, which affects approximately 4% of patients following major noncardiac surgery.<sup>95</sup> The overall incidence of new postoperative atrial arrhythmias may be as high as 10% in this patient population. The incidence is even higher after cardiac and thoracic procedures when the cardiac arrhythmia is often attributed to atrial irritation.<sup>96</sup> The risk of postoperative atrial fibrillation is increased by preexisting cardiac risk factors, positive fluid balance, electrolyte abnormalities, and oxygen desaturation.<sup>97</sup> These new-onset atrial arrhythmias are not benign as they are associated with a longer hospital stay and increased mortality.<sup>98,99</sup>

Control of the ventricular response rate is the immediate goal in the treatment of new-onset atrial fibrillation. Hemodynamically unstable patients may require prompt electrical cardioversion, but most patients can be treated pharmacologically with an intravenous  $\beta$ -adrenergic blocker or calcium channel blocker.<sup>100</sup> If hemodynamic instability is a concern, the short-acting  $\beta$ -blocker esmolol can be considered. Rate control with these agents is often enough to chemically cardiovert the postoperative patient whose arrhythmia may be catecholamine driven. If the goal of therapy is chemical cardioversion, an amiodarone load can be initiated in the PACU with the knowledge that QT prolongation, bradycardia, and hypotension may accompany the intravenous infusion of this drug.

## VENTRICULAR ARRHYTHMIAS

Premature ventricular contractions (PVCs) and ventricular bigeminy commonly occur in the PACU. PVCs most often reflect increased sympathetic nervous system stimulation that may accompany tracheal intubation, pain, and transient hypercapnia. They commonly resolve on their own, but this can be facilitated by administering analgesics and ensuring proper ventilation. True ventricular tachycardia is rare and is indicative of underlying cardiac pathology. In the case of torsades de pointes (polymorphic ventricular tachycardia), underlying QT prolongation on the ECG may be intrinsic or drug related. The most commonly administered QT prolonging drugs in PACU are 5-HT3 receptor antagonists (e.g., ondansetron, dolasetron), haloperidol, droperidol, albuterol, methadone, and amiodarone. Treatment with 1 to 2 g of magnesium IV over 5 minutes should be initiated and potentially repeated, if necessary.

## TREATMENT

Early postoperative arrhythmias often require immediate electrolyte correction as well as pharmacologic and non-pharmacologic interventions.<sup>101</sup> In general, the urgency of treatment of a cardiac arrhythmia depends on the physiologic consequences of the arrhythmia, basically hypotension, cardiac ischemia, or both. Tachyarrhythmias decrease coronary perfusion time and increase myocardial oxygen consumption. Their impact depends on the patient's underlying cardiac function, and they are most harmful in patients with coronary artery disease. Bradycardia has a more deleterious effect in patients with a fixed stroke volume, such as infants and patients with restrictive pericardial disease or cardiac tamponade. For the most part, treatment relies on identifying and correcting the underlying cause (i.e., hypoxemia or electrolyte abnormalities).<sup>102</sup> The possible role of myocardial ischemia or the occurrence of pulmonary embolism must be considered when contemplating treatment options.

## Renal Dysfunction

The differential diagnosis of postoperative renal dysfunction includes prerenal, intrarenal, and postrenal etiologies (Box 80.8). Frequently, the cause of renal insufficiency in the postoperative period is multifactorial, with an intraoperative insult exacerbating a preexisting renal insufficiency.<sup>103-106</sup> In the PACU, diagnostic efforts should focus on the identification and treatment of the readily reversible causes of oliguria (i.e., urine output less than 0.5 mL/kg/h). For example, urinary catheter obstruction or dislodgment is easily remedied and often overlooked (see Box 80.8). When appropriate, one should confer with the surgical team regarding the details of the surgical procedure (urologic or gynecologic) to rule out anatomic obstruction or disruption of the ureters, bladder, or urethra.

Patient-related factors play a role in the development of acute kidney injury (AKI) in the postoperative period. Comorbidities, such as preexisting renal insufficiency (CKD), diabetes mellitus, hypertension, morbid obesity, history of steroid use, male sex, and old age, are a number of

## BOX 80.8 Postoperative Oliguria

### Prerenal

Hypovolemia (bleeding, sepsis, third-space fluid loss, inadequate volume resuscitation)  
Hepatorenal syndrome  
Low cardiac output  
Renal vascular obstruction or disruption  
Intraabdominal hypertension

### Renal

Ischemia (acute tubular necrosis)  
Radiographic contrast dyes  
Rhabdomyolysis  
Tumor lysis  
Hemolysis

### Postrenal

Surgical injury to the ureters  
Obstruction of the ureters with clots or stones  
Mechanical (urinary catheter obstruction or malposition)

may be needed as an adjunct to fluid therapy in hypotensive patients. To date, there is no evidence that one vasoconstrictor is superior to another. It should be noted that even though low-dose dopamine can increase urine output, it is no longer deemed to be renoprotective and is not endorsed as a treatment strategy in AKI. Furthermore, vasodilator therapy (fenoldopam, atrial natriuretic peptide) is also not recommended in AKI prevention or treatment.

## OLIGURIA

### Intravascular Volume Depletion

The most common cause of oliguria in the immediate postoperative period is intravascular volume depletion. If the patient also demonstrates signs of hypovolemia, such as tachycardia and hypotension, a fluid challenge (500-1000 mL of crystalloid) is usually effective in restoring urine output. A CBC should be drawn if ongoing surgical blood loss is suspected and repeated fluid boluses are required to maintain adequate urine output. Patients with a history of hypertension may require higher MAPs to produce adequate urine. Their kidneys may not be perfused adequately with the standard “MAP > 65.” In this patient population, it is imperative to review their baseline blood pressures and target a MAP greater than 75 mm Hg to ensure renal perfusion. Volume resuscitation to maximize renal perfusion is particularly important to prevent ongoing ischemic injury and the development of acute tubular necrosis. However, urine output does not predict the likelihood of developing postoperative AKI.

If a fluid challenge is contraindicated or oliguria persists, then assessment of intravascular fluid volume status and cardiac function is indicated to differentiate hypovolemia from sepsis and low cardiac output states. Fractional excretion of sodium can be useful in determining the adequacy of renal perfusion, assuming that diuretics have not been given. However, the diagnosis of prerenal azotemia will not differentiate hypovolemia, congestive heart failure, or hepatorenal syndrome. Further evaluation with central venous monitoring or echocardiography, or both, may facilitate the differential diagnosis.

### Postoperative Urinary Retention

Postoperative urinary retention can cause bladder overdistention and permanent detrusor damage. Ultrasonography can measure bladder volume and identify urinary retention in the PACU.<sup>111</sup> Using this technique, Keita and associates attempted to identify patients at high risk by measuring bladder volume in 313 adult inpatients on admission to and before discharge from the PACU. They collected data on age, sex, history of urinary retention, intraoperative administration of anticholinergic agents, amount of intraoperative fluid administration, and intravenous use of morphine. Urinary retention was defined as bladder volume greater than 600 mL in conjunction with an inability to void within 30 minutes. In this study, the incidence of postoperative urinary retention in the PACU was 16%. The most significant predictive factors were age older than 50 years, intraoperative fluid more than 750 mL, and bladder volume on entry to the PACU greater than 270 mL.<sup>112</sup> This study argues for the use of ultrasound to identify patients at high risk for possible urinary retention.

issues that should be taken into account when determining whether a patient is at an increased risk of perioperative renal dysfunction. In addition to nonmodifiable patient risk factors, the surgical procedure itself also comprises an independent risk factor in the development of perioperative renal dysfunction, with cardiac surgery, emergency surgery, and “major” surgery (vascular, transplant, thoracic) all serving to increase the probability.

A number of perioperative events may alter renal perfusion. Preoperative or intraoperative angiography can result in ischemic injury, secondary to renal vasoconstriction and direct renal tubular injury. Perioperative volume depletion can exacerbate hepatorenal syndrome or acute tubular necrosis caused by sepsis. The surgical procedure itself can alter renal vascular patency, decreasing renal perfusion. Finally, increased intraabdominal pressure (IAP) can impair renal perfusion.

Judicious intraoperative fluid management is of utmost importance both during the surgical procedure and in the postoperative period. Hemodynamics must be monitored to ensure that relative intravascular volume is sufficient to allow for tissue perfusion and avoidance of organ hypoxia and dysfunction. Crystalloid solutions are ubiquitous in the operating room and PACU. Balanced solutions (lactated Ringers, Plasmalyte) may be superior to chloride-only containing solutions (NaCl), as hyperchloraemia is associated with the development of AKI.<sup>107</sup> A study published in Critical Care in 2014 revealed that chloride-liberal fluid administration was a risk factor in the development of postoperative AKI in liver transplant patients.<sup>108</sup> In general, hydroxylethyl starch solutions should be avoided, as there lacks any clear benefit to their use.<sup>109</sup>

A recent study published in Anesthesiology demonstrated that the risk of developing postoperative AKI was increased when the MAP was less than 60 for greater than 20 minutes or less than 55 for greater than 10 minutes.<sup>110</sup> As stated above, given the changes in renal autoregulation that occur over time in patients with hypertension, MAP goals should be tailored to each patient. Vasopressors

## CONTRAST NEPHROPATHY

Patients who have undergone angiography  $+$ / $-$  intravascular stent placement for carotid stenosis, thoracic and abdominal aortic aneurysms, peripheral vascular disease, and cerebral aneurysms are increasing in numbers in our PACUs. As a result, contrast nephropathy should always be considered in the differential diagnosis of postoperative renal dysfunction and prompt diagnosis is crucial, as contrast nephropathy, in general, is one of the reversible causes of postoperative AKI. The creatinine tends to increase within 24 to 48 hours following the administration of contrast media, however return to the patient's baseline typically occurs within one week. Perioperative attention to adequate hydration is indicated in any patient who has received an intravenous contrast agent. Aggressive hydration with a balanced crystalloid solution is the single most effective means of protection against contrast nephropathy. Alkalization of the urine with a sodium bicarbonate infusion and Mucomyst are sometimes used as well; however, beneficial evidence of these therapies is lacking and not well established.<sup>113</sup>

## INTRAABDOMINAL HYPERTENSION

Intraabdominal hypertension (IAH) should be considered in any patient with oliguria and a tense abdomen on examination after abdominal surgery.<sup>114,115</sup> Elevated IAP can impede renal perfusion and lead to renal ischemia and postoperative renal dysfunction. Normal IAP in a patient who is not obese is approximately 5 mm Hg. Intraabdominal hypertension is graded into four categories: I: 12 to 15 mm Hg; II: 16 to 20 mm Hg; III: 21 to 25 mm Hg; and IV: greater than 25 mm Hg. Abdominal compartment syndrome is defined as an IAP greater than 20 mm Hg with or without an abdominal perfusion pressure less than 50 mm Hg.<sup>116</sup> Abdominal compartment syndrome (IAP usually  $>25$  mm Hg) should be considered in patients with IAH that are exhibiting signs of new end organ dysfunction. In a prospective study of patients undergoing major abdominal surgery, intraabdominal hypertension accounted for 40% of new-onset renal insufficiency. In this study, postoperative renal impairment was independently associated with four factors: hypotension, sepsis, older age, and increased abdominal pressure.<sup>117</sup>

Elevation of IAP impairs venous drainage from the kidney, secondary to the increased vascular resistance that ensues when the renal vein is compressed. This cascade of events is responsible for the renal dysfunction that ultimately arises. When IAP reaches 15 mm Hg, oliguria tends to develop, whereas anuria is not common until pressures reach approximately 30 mm Hg. Management and treatment are mainly supportive (limiting extraneous fluids); however in severe cases, surgical decompression of the abdomen may be required.

Bladder pressure, an indirect assessment of IAP, should be measured in patients in whom intraabdominal hypertension is suspected to ensure the initiation of prompt intervention to relieve the pressure and therefore restore renal perfusion. Bladder pressure is measured at end expiration

with the patient in the supine position and in the absence of abdominal muscle contractions. As with arterial pressure measurements, the transducer is placed in the midaxillary line.<sup>117</sup>

## RHABDOMYOLYSIS

Rhabdomyolysis may complicate the postoperative course of patients who have suffered major crush or thermal injury. Patients may complain of myalgias, abdominal pain, nausea, and weakness. Myoglobinuria may be present and creatine kinase (CK) levels are elevated. The incidence is also significantly increased in morbidly obese patients undergoing bariatric surgery. Rhabdomyolysis has been reported to occur in 22.7% of 66 consecutive patients undergoing laparoscopic bariatric surgery.<sup>118-121</sup> Risk factors include increased BMI and the length of the surgery. Patient history and the operative course should guide the decision to measure creatine phosphokinase in the PACU.<sup>119</sup> Early, aggressive hydration to maintain urine output is the mainstay of treatment, as hypovolemia only serves to further intensify the impending renal failure secondary to renal ischemia and tubular obstruction from the heme casts. Electrolyte abnormalities, including hyperkalemia, hyperphosphatemia, and hypocalcemia must be detected and corrected immediately. Loop diuretics can be used to flush the renal tubules and to avoid fluid overload. The infusion of mannitol to enhance the elimination of myoglobin casts from the renal tubules and bicarbonate to protect against myoglobin toxicity is commonly practiced but may not provide further benefit. In a study of more than 2000 trauma patients with rhabdomyolysis, the infusion of bicarbonate and mannitol did not further decrease the incidence of acute renal failure.<sup>121</sup> In severe cases, an attempt can be made to remove myoglobin by continuous renal replacement therapy. Unlike conventional hemodialysis filters that do not remove circulating myoglobin, high-flux membranes can be effective. Continuous renal replacement modes typically use high-flux membranes. Additionally, convection (i.e., the mechanism of solute removal in continuous hemofiltration) removes larger molecular weight solutes than diffusion (i.e., the mechanism of solute removal in conventional hemodialysis).<sup>122</sup>

## Postoperative Hypothermia and Shivering

Postoperative hypothermia, defined as a core temperature less than 36°C, is a detrimental and unpleasant condition that can occur after general and neuraxial anesthesia. According to the American Society of Anesthesiologists, the patient's temperature should be measured within 15 minutes after anesthesia end time and ideally be at least 36°C.<sup>123</sup> Postoperative shivering also often occurs after general and neuraxial anesthesia. The incidence of postoperative shivering may be as high as 66% after general anesthesia.<sup>124</sup> Identified risk factors include young age, endoprosthetic surgery, and core hypothermia.<sup>125</sup>

## MECHANISM

Postoperative hypothermia occurs secondary to heat loss during surgery. Underlying mechanisms are radiation, convection, evaporation, and conduction.<sup>126</sup> Postoperative shivering is usually, but not always, associated with hypothermia. Although thermoregulatory mechanisms can explain shivering in the hypothermic patient, a number of different mechanisms have been proposed to explain shivering in normothermic patients. One proposed mechanism is based on the observation that the brain and spinal cord do not recover simultaneously from general anesthesia. The more rapid recovery of spinal cord function is thought to result in uninhibited spinal reflexes manifested as clonic activity. This theory is supported by the fact that doxapram, a central nervous system stimulant, is somewhat effective in abolishing postoperative shivering. Other proposed mechanisms include the action of kappa opioid, N-methyl-D-aspartate (NMDA), and 5-hydroxytryptamine receptors. The higher incidence of postanesthetic shivering in patients who receive high-dose remifentanil is thought to be by the same mechanism that causes hyperalgesia in these patients—sudden opioid withdrawal resulting in the stimulation of NMDA receptors.<sup>127</sup> Additional support for this theory comes from the same authors who found that a small dose of intraoperative ketamine reduced the incidence of remifentanil-induced postanesthetic shivering.<sup>128</sup> Tramadol, a weak  $\mu$ -opioid receptor agonist, and norepinephrine and serotonin reuptake inhibitor, has been shown to be effective in preventing postoperative shivering while also contributing to analgesia.<sup>129</sup>

## TREATMENT

Intervention includes the identification and treatment of hypothermia if present. Accurate core body temperatures can be most easily obtained at the tympanic membrane. Axillary, rectal, and nasopharyngeal temperature measurements are less accurate and may underestimate core temperature. Forced air warmers are used to actively warm the hypothermic patient. A number of opioids, ondansetron,<sup>130</sup> clonidine,<sup>131</sup> and ketamine<sup>132</sup> have been shown to be effective in abolishing shivering once it starts. Of those, meperidine, 12.5–25 mg IV, is most commonly used in adults. The intraoperative infusion of dexmedetomidine has been shown to be an effective prophylactic measure.<sup>133</sup>

## CLINICAL EFFECTS

In addition to significant patient discomfort, so-called thermal discomfort, postoperative shivering increases oxygen consumption,  $\text{CO}_2$  production, and sympathetic tone. It is associated with increased cardiac output, heart rate, systemic blood pressure, and intraocular pressure. Patients who are hypothermic on arrival in the PACU should be actively warmed to avoid these immediate complications as well as delayed consequences of hypothermia. Mild to moderate hypothermia ( $33^{\circ}\text{C}$ – $35^{\circ}\text{C}$ ) inhibits platelet function, coagulation factor activity, and drug metabolism. It exacerbates postoperative bleeding, prolongs neuromuscular

blockade, and may delay awakening. Whereas these immediate consequences are associated with a prolonged PACU stay,<sup>134</sup> long-term deleterious effects include an increased incidence of myocardial ischemia and myocardial infarction, delayed wound healing, and increased perioperative mortality.

## Postoperative Nausea and Vomiting

Without prophylactic intervention, roughly one third of patients who undergo inhalational anesthesia will develop PONV (range, 10%–80%).<sup>135,136</sup> The consequences of PONV include delayed discharge from the PACU, unanticipated hospital admission, increased incidence of pulmonary aspiration, and significant postoperative discomfort. The ability to identify high-risk patients for prophylactic intervention can significantly improve the quality of patient care and satisfaction in the PACU. From a patient's perspective, PONV may be more uncomfortable than postoperative pain.

## PREVENTION AND TREATMENT

Prophylactic measures to prevent PONV include modification of anesthetic technique and pharmacologic intervention. In a randomized controlled multicenter multifactorial trial, Apfel and associates studied the efficacy of six prophylactic interventions in high-risk patients (PONV risk  $> 40\%$ ).<sup>135</sup> Interventions were both pharmacologic and technique related. Pharmacologic intervention included droperidol, 1.25 mg; dexamethasone, 4 mg; or ondansetron, 4 mg. Anesthetic intervention included propofol in lieu of volatile anesthetic, nitrogen in lieu of nitrous oxide, or remifentanil in lieu of fentanyl. More than 4000 patients were assigned to 1 of 64 possible combinations. The study found that each of the three antiemetics reduced the relative risk of PONV to the same degree (26%). Together, propofol (19% decrease) and nitrogen (12% decrease) reduced the relative risk of PONV to a similar degree.

Although prophylactic measures to prevent PONV are more effective than rescue measures, a subset of patients will require treatment in the PACU even after appropriate prophylactic treatment. There is no convincing evidence that any of the serotonin receptor antagonists commonly prescribed at this time are more effective than any others. **Box 80.9** lists the different classes of antiemetic medications commonly prescribed for prophylaxis as well as treatment of PONV in the PACU. If an adequate dose of antiemetic given at the appropriate time is ineffective, simply giving more of the same class of drug in the PACU is unlikely to produce any significant benefit. Therefore, it is not recommended to redose any medication of the same class within 6 hours after the initial dose. Specific antiemetic medications such as scopolamine, dexamethasone, and aprepitant should not be redosed at all.<sup>136</sup>

The likelihood of a patient experiencing PONV depends on several risk factors and increases with the number of those factors that the patient possesses. Apfel et al. identified female gender, non-smoker, history of PONV/motion

### BOX 80.9 Commonly Used Antiemetics (Adult Doses)

#### Anticholinergics

Scopolamine (1.5 mg) transdermal patch to a hairless area behind the ear before surgery (remove 24 h postoperatively)

#### NK-1 receptor antagonist

Aprepitant (40 mg per os within 3 h prior to anesthesia)

#### Corticosteroids

Dexamethasone (4 mg IV after induction of anesthesia)

#### Antihistamines

Hydroxyzine (12.5-25 mg IM)

Diphenhydramine (25-50 mg IV)

#### Phenothiazines

Promethazine (12.5-25 mg IM)

Prochlorperazine (5-10 mg IV)

#### Butyrophenones

Droperidol (0.625-1.25 mg IV); monitor the ECG for prolongation of the QT interval for 2-3 h after administration; preoperative 12-lead ECG recommended

Haloperidol (0.5- $<2$  mg IM/IV)

#### Prokinetic

Metoclopramide (10-20 mg IV; avoid if any possibility of gastrointestinal obstruction)

#### Serotonin Receptor Antagonists

Ondansetron (4 mg IV 30 min before the conclusion of surgery)

#### Vasopressors

Ephedrine (25 mg IM, combined with hydroxyzine, 25 mg)

sickness, and the need for postoperative opioids as independent risk factors. Their group has created a simplified risk score which predicts a likelihood to develop PONV of 10% for patients with no risk factor, 20% with 1 risk factor, 40% with 2 risk factors, 60% with 3 risk factors, and 80% with all four risk factors. More recently, the same author identified young age, defined as age below 50 years, as another independent risk factor for postdischarge nausea and vomiting.<sup>137</sup> The Society of Ambulatory Anesthesia published "Consensus Guidelines for the Management of Postoperative Nausea and Vomiting,"<sup>136</sup> which provides a great overview of the topic. The Prevention of PONV was added to the Physician Quality Reporting System of the Centers for Medicare and Medicaid Services. The goal is to give at least two different antiemetics to every patient older than 18 years undergoing any procedure under inhalational general anesthesia, if they have at least three risk factors for PONV.<sup>138</sup>

Emend (aprepitant), a substance P/neurokinin 1 receptor antagonist, may be effective in very high-risk patients and refractory cases. The recommended dose is 40 mg by mouth within 3 hours prior to anesthesia. Initial clinical trials have shown the drug to be effective for up to 48 hours after surgery.<sup>139</sup>

## Delirium

Postoperative delirium (POD) is defined as an acute and fluctuating alteration of mental state of reduced awareness and disturbance of attention. POD often starts in the recovery room and can occur up to 5 days after surgery. One study found that many patients who were diagnosed with POD on the floor already had POD in the recovery room. The incidence of POD depends on peri- and intraoperative risk factors and is highly variable, for example, a meta-analysis of 26 studies of POD found an incidence ranging from 4.0% to 53.3% in hip fracture patients.<sup>140</sup> Multiple studies across different surgical specialties in elective and emergency cases have shown that POD is associated with worse surgical outcomes, increased hospital length of stay, functional decline, higher rates of institutionalization, higher mortality, and higher cost and resource utilization.<sup>141</sup> It is important to distinguish between the hyperactive and the hypoactive subtype of delirium, since the latter may easily go unnoticed, be therefore untreated, and potentially linked to a worse outcome.<sup>142</sup>

## RISK FACTORS

POD has been linked to multiple risk factors. These are commonly distinguished between predisposing factors (inherent to the patient) and precipitating factors (triggering the onset of delirium). Major predisposing patient risk factors include (1) age greater than 65 years, (2) cognitive impairment, (3) severe illness or comorbidity burden, (4) hearing or vision impairment, and (5) presence of infection.<sup>143</sup> In the perioperative context, the performed surgical procedure acts as a physiologic stressor with the extent of surgery having a major impact on the likelihood of developing delirium. Risk assessment is a shared clinical responsibility and should ideally be implemented in a perioperative clinical pathway.

## PROPHYLAXIS AND MANAGEMENT

Patients at high risk of POD should ideally be identified prior to entering the operating room by using a delirium risk screening tool. Patients who screen positive should potentially go on a delirium reduction pathway to decrease their likelihood of developing delirium in the postoperative phase. Once in the recovery room, any deliriogenic medications should be avoided (e.g., anticholinergics, sedative-hypnotics, meperidine), unless the specific needs for any of these medications outweigh their potential risks (e.g., benzodiazepines for benzodiazepine or alcohol withdrawal).<sup>144</sup> Simple measures, such as frequent reorientation, sensory enhancement (ensuring glasses, hearing aids, or listening amplifiers are available upon arrival in the PACU), pain control, cognitive stimulation, simple communication standards and approaches to prevent the escalation of behaviors, and keeping the patients in their circadian rhythm can decrease the incidence of developing POD by 30% to 40%.<sup>144</sup> Screening for delirium in the PACU should be performed before the patient leaves the unit (e.g., with the Nursing Delirium Screening Scale or Confusion Assessment Method score).

If prevention has failed and the patient screens positive, prompt evaluation of possible precipitating factors should occur. These include uncontrolled pain, hypoxia, pneumonia, infection (wound, indwelling catheter and blood stream, urinary tract, sepsis), electrolyte abnormalities, urinary retention, fecal impaction, medications, and hypoglycemia.<sup>141</sup> Treatment of causative factors and symptoms has a major impact on reducing the duration of delirium and should therefore be initiated immediately. Generally, multicomponent nonpharmacologic interventions should be used for all delirious patients (e.g., frequent reorientation, calm environment, eliminating restraint use, familiar objects in the room, bringing glasses and hearing aids to the patient). Pharmacologic interventions should be reserved and only used in the lowest effective dose for agitated delirious patients when other interventions have failed and the patients pose a substantial harm to themselves or others. The medication of choice in this case is haloperidol starting at 0.5 to 1 mg IM/IV. Alternatively, atypical antipsychotics like risperidone, olanzapine, quetiapine, or ziprasidone can also be considered.<sup>141</sup>

## Emergence Excitement

Persistent POD should not be confused with emergence “excitement,” a transient confusional state that is associated with emergence from general anesthesia. Emergence excitement is common in children, with more than 30% experiencing agitation or delirium at some period during their PACU stay. It usually occurs within the first 10 minutes of recovery but can have onset later in children who are brought to the recovery room asleep. The peak age of emergence excitement in<sup>145</sup> children is between 2 and 4 years. Unlike delirium, emergence excitement typically resolves quickly and is followed by uneventful recovery.<sup>146</sup>

In children, emergence excitement is most frequently associated with rapid “wake up” from inhalational anesthesia. Although it has also been reported after isoflurane<sup>147</sup> and, to a lesser extent, halothane<sup>148</sup> anesthesia, it is most often associated with the less-soluble vapors sevoflurane<sup>149</sup> and desflurane. Several studies suggest that the incidence of emergence excitement is more a reflection of the anesthetic agent used rather than the rapidity of emergence.<sup>150</sup> In studies comparing sevoflurane and propofol, propofol resulted in a much smoother awakening than sevoflurane despite rapid emergence. Furthermore, delaying emergence by a slow reduction in the inhaled concentration of sevoflurane did not reduce the incidence of emergence excitement.<sup>151</sup>

In addition to rapid emergence, the literature supports a number of possible etiologic factors, including intrinsic characteristics of the anesthetic, postoperative pain, type of surgery, age, preoperative anxiety, underlying temperament, and adjunct medications. Awareness of these contributors allows one to identify and treat children who are at increased risk.<sup>146</sup>

Simple preventative measures should be taken to treat children at risk. These include reducing preoperative anxiety, treating postoperative pain, and providing a stress-free

environment for recovery. Medications that have been used to prevent and treat emergence agitation/delirium in children include midazolam,<sup>152</sup> clonidine,<sup>153-155</sup> dexmedetomidine,<sup>156,157</sup> fentanyl,<sup>158,159</sup> ketorolac,<sup>160</sup> and physostigmine.<sup>161</sup> In children, the most common preoperative anxiolytic, midazolam, has produced conflicting data. Although midazolam is generally associated with a decrease in the incidence and duration of POD, not all studies are in agreement. In studies in which it has not been shown to be beneficial, it is unclear whether midazolam is an independent factor or merely a reflection of other preoperative variables.<sup>162</sup>

The incidence of emergence excitement in adults is significantly less than in children. It is estimated to be between 3% and 4.7%.<sup>163</sup> One study found that significant surgical- and anesthesia-related risk factors included preoperative medication with midazolam (OR 1.9), breast surgery (OR 5.2), abdominal surgery (OR 3.2), and, to a much lesser extent, length of surgery.<sup>163</sup>

## Delayed Awakening

Even after prolonged surgery and anesthesia, a response to stimulation in 60 to 90 minutes should occur.<sup>164</sup> If emergence has not taken place at that point, it is important to consider multiple different reasons as the possible underlying cause. Residual drug effects are the most frequent cause of delayed emergence and may occur after too much anesthetic has been given or in a patient who is susceptible to the side effects of certain medications due to age, underlying disease, or metabolic derangements. The most common drugs to consider are benzodiazepines, opioids, and neuromuscular blocking drugs, however, after a very long anesthetic, propofol and volatile anesthetics can also cause a delay in emergence. Furthermore, acute alcohol or illicit drug intoxication can be other culprits. Another often overlooked drug effect is the central anticholinergic syndrome (CAS). Several drugs used during anesthesia can block the central cholinergic neurotransmission and therefore delay the wakeup.<sup>165</sup> Metabolic disturbances such as hypothermia (<33°C), electrolyte imbalances (e.g., hyponatremia, hypercalcemia, hypermagnesemia), hypo- or hyperglycemia, as well as underlying metabolic diseases (e.g., liver, kidney, or thyroid abnormalities) can delay emergence after anesthesia. Finally, neurologic complications such as cerebral hypoxia, seizures (with consecutive postictal state), elevated ICP, as well as any intracerebral event (hemorrhage, thrombosis, embolus) should be considered.<sup>166,167</sup>

In any patient who presents with a delayed emergence, airway, breathing, and circulation should be assessed. It is important to confirm that all anesthetic agents are discontinued (including residual agents left in the IV tubing). The patient’s body temperature should be checked upon arrival in the PACU and if hypothermia is present, the patient should be actively rewarmed. A cardiopulmonary as well as a neurologic exam (including pupils, cough and gag reflex, motor/strength) should be performed. The use of a neuromuscular transmission monitor (TOF, ideally TOF-R) is instrumental in detecting residual neuromuscular blockade, which should be reversed (with either

neostigmine/glycopyrrolate or sugammadex). If a residual opioid effect is suspected, naloxone in small increments (40 µg every 2 minutes up to 200 µg) can be titrated to effect. Equally, if a residual benzodiazepine effect is suspected, flumazenil in 0.1 to 0.2 mg increments every 1 minute up to 1 mg can be titrated to effect. A blood glucose level should be checked and hypoglycemia should be treated with dextrose, whereas hyperglycemia can be treated with insulin as needed. An ABG and electrolyte panel should be obtained. CO<sub>2</sub> narcosis can be treated with hyperventilation (and potentially intubation), and electrolyte disturbances should be corrected. If none of the above interventions yields any suspicious results, CAS should be considered and physostigmine 1 to 2 mg IV could be administered. At the same time, it is important to rule out any cerebrovascular accident by consulting neurology and obtaining a stat head CT. If the patient still does not emerge, admission to the ICU for further monitoring and serial exams should be initiated.

## Discharge Criteria

Although specific PACU discharge criteria may vary, certain general principles are universally applicable (Box 80.10).<sup>2</sup> To summarize, a mandatory minimum stay in the PACU is not required. Patients must be observed until they are no longer at risk for ventilatory depression and their mental status is clear or has returned to baseline. Hemodynamic criteria are based on the patient's baseline hemodynamics without specific systemic blood pressure and heart rate requirements. An assessment and written documentation of the patient's peripheral nerve function on discharge from the PACU may become useful information should a new peripheral neuropathy develop in the later postoperative period.

## POSTANESTHESIA SCORING SYSTEMS

In 1970, Aldrete and Kroulik developed a postanesthesia scoring system to monitor recovery from anesthesia. The original Aldrete score assigned a number of 0, 1, or 2 to 5 variables: activity, respiration, circulation, consciousness, and color. A score of 9 out of 10 was considered adequate for discharge from the PACU.<sup>168</sup> Over the years, this system has been modified to keep up with advances in technology and anesthesia practice, including the expansion of ambulatory surgery. In 1995, pulse oximetry replaced visual assessment of oxygenation and additional assessments were added to accommodate patients undergoing ambulatory surgery (Tables 80.3 and 80.4).<sup>169</sup>

With the increase in number and complexity of outpatient surgeries, discharge criteria have been amended by various authors to include assessment of home readiness. The resulting PADSS, or postanesthesia discharge scoring system, continues to evolve. It was initially based on five criteria: vital signs, ambulation and mental status, pain and nausea/vomiting, surgical bleeding, and fluid intake/output. The current version has been modified to separate pain and nausea/vomiting and to eliminate the need to urinate before discharge.<sup>170-174</sup> In the ambulatory

### BOX 80.10 Summary of Recommendations for Discharge

1. Patients should be alert and oriented or mental status returned to baseline.
2. A minimum mandatory stay is not required.
3. Vital signs should be stable and within acceptable limits.
4. Discharge should occur after patients have met specified criteria.
5. Use of scoring systems may assist in documenting fitness for discharge.
6. The requirement to urinate before discharge and drink and retain clear liquids should *not* be part of a routine discharge protocol, although these requirements may be appropriate for selected patients.
7. Outpatients should be discharged to a responsible adult who will accompany them home.
8. Outpatients should be provided with written instructions regarding postprocedure diet, medications, activities, and a telephone number to call in case of emergency.

Modified from American Society of Anesthesiologists Task Force on Postanesthetic Care. Practice Guidelines for Postanesthetic Care: a report by the American Society of Anesthesiologists Task Force on Postanesthetic Care. *Anesthesiology*. 2002;96:742-752.

**TABLE 80.3** Criteria for the Determination of Discharge Score for Release from the Postanesthesia Care Unit

Variable Evaluated	Score
<b>ACTIVITY</b>	
Able to move four extremities on command	2
Able to move two extremities on command	1
Able to move no extremities on command	0
<b>BREATHING</b>	
Able to breathe deeply and cough freely	2
Dyspnea	1
Apnea	0
<b>CIRCULATION</b>	
Systemic blood pressure $\leq$ 20% of the preanesthetic level	2
Systemic blood pressure is 20% to 50% of the preanesthetic level	1
Systemic blood pressure $\geq$ 50% of the preanesthetic level	0
<b>CONSCIOUSNESS</b>	
Fully awake	2
Arousable	1
Not responding	0
<b>OXYGEN SATURATION (PULSE OXIMETRY)</b>	
Greater than 92% while breathing room air	2
Needs supplemental oxygen to maintain saturation $>90\%$	1
Less than 90% with supplemental oxygen	0

Modified from Aldrete JA. The postanaesthesia recovery score revisited. *J Clin Anesth*. 1995;7:89-91.

**TABLE 80.4** Criteria for Determination of Discharge Score for Release Home to a Responsible Adult

Variable Evaluated	Score*
<b>VITAL SIGNS (STABLE AND CONSISTENT WITH AGE AND PREANESTHETIC BASELINE)</b>	
Systemic blood pressure and heart rate within 20% of the preanesthetic level	2
Systemic blood pressure and heart rate 20% to 40% of the preanesthetic level	1
Systemic blood pressure and heart rate >40% of the preanesthetic level	0
<b>ACTIVITY LEVEL (ABLE TO AMBULATE AT PREOPERATIVE LEVEL)</b>	
Steady gait without dizziness or meets the preanesthetic level	2
Requires assistance	1
Unable to ambulate	0
<b>NAUSEA AND VOMITING</b>	
None to minimal	2
Moderate	1
Severe (continues after repeated treatment)	0
<b>PAIN (MINIMAL TO NO PAIN, CONTROLLABLE WITH ORAL ANALGESICS; LOCATION, TYPE, AND INTENSITY CONSISTENT WITH ANTICIPATED POSTOPERATIVE DISCOMFORT)</b>	
Acceptability:	
Yes	2
No	1
<b>SURGICAL BLEEDING (CONSISTENT WITH THAT EXPECTED FOR THE SURGICAL PROCEDURE)</b>	
Minimal (does not require dressing change)	2
Moderate (up to two dressing changes required)	1
Severe (more than three dressing changes required)	0

\*Patients achieving a score of at least 9 are acceptable for discharge.

Modified from Marshall SI, Chang F. Discharge criteria and complications after ambulatory surgery. *Anesth Analg*. 1999;88:508-517.

surgery setting, postoperative pain is the most significant cause of delayed discharge and unplanned hospital admission. In an effort to improve patient satisfaction and timely discharge, Chung and associates identified a subset of high-risk patients who are likely to benefit from intense prophylactic analgesic therapy. This study of 10,008 consecutive ambulatory surgical patients found that the incidence and intensity of postoperative pain increased with increasing BMI and duration of anesthesia. Orthopedic and urologic procedures were the most significant surgical factors.<sup>175</sup>

PACU Standards of Care require that a physician accept responsibility for the discharge of patients from the unit (Standard V).<sup>1</sup> This is the case even when the decision to discharge the patient is made at the bedside by the PACU nurse in accordance with hospital-sanctioned discharge criteria or scoring systems. If discharge criteria are to be used, they must first be approved by the department of anesthesia and the hospital medical staff. A responsible physician's name must be noted on the record.

## Infection Control

Limitations in space,<sup>161</sup> staffing,<sup>176,177</sup> and time contribute to the transmission of infectious organisms in the PACU. The PACU is typically an open unit without physical barriers between bed stations, however many units, such as those at Massachusetts General Hospital (MGH), have transitioned to individual rooms with doors. There are also a number of both positive and negative pressure specific rooms. Nurses and respiratory therapists simultaneously care for more than one patient, and admissions to the unit are transient with a length of stay measured in hours rather than days. Infection control monitoring can be difficult, as an infection that is transmitted as a result of a lapse in proper infection control in the PACU might not be identified by routine monitoring until days later on the inpatient unit.

Standard precautions, which are known as the absolute minimum method of infection control, should always be followed when encountering each patient.<sup>178,179</sup> Hand hygiene, which encompasses washing the hands with an antimicrobial soap or the use of alcohol-based hand rub (ABHR), is the single most important and effective component of preventing contamination between patients and should be employed both before and after patient contact.<sup>180,181</sup> Proper hand hygiene is required even if the caregiver is wearing gloves. The installation of bedside alcohol-based cleansers increases compliance of hand hygiene among healthcare workers in the ICU.<sup>182-185</sup> Although no equivalent study has been conducted in the PACU, the unit is similar to the ICU in workload and intensity of patient care. The Centers for Disease Control and Prevention's Guideline for Hand Hygiene in Health-Care Settings recommends that an "alcohol based hand rub [be made] available at the entrance to the patient's room or at the bedside, in other convenient locations, and in individual pocket-sized containers to be carried by [healthcare workers] HCWs."<sup>186</sup> Although the convenience of appropriately placed alcohol-based cleansers is expected to improve hand-cleansing compliance, no follow-up studies in the PACU have been published.

With these limitations in mind, it is not surprising that the PACU has been described as the "weakest link" in the chain of care that bridges the sterile technique practiced in the operating room with infection control protocols practiced on the surgical unit. Despite an awareness of the factors that increase the risk of infection in the PACU, no studies have addressed the problem until recently. A study of hand cleansing during postanesthesia care documents the poor compliance of PACU nurses with this standard infection control procedure.<sup>182,187</sup> In this observational study of 3143 patient care activities, the average compliance with hand cleansing was only 19.6% on patient admission to the unit and 12.5% in patients already admitted to the unit. In this study, the intensity of patient care activities was an independent predictor of noncompliance; that is, the greater the workload, the less likely the nursing staff would comply with infection control measures. Additional independent factors included patients of advanced age (65 years and older) and those recovering from clean surgery (i.e., surgical sites in which the respiratory, alimentary, and urinary tracts are not entered) and clean-contaminated surgery (i.e., surgical sites in which

**TABLE 80.5** Infectious Agent Precautions

Droplet Precautions	Airborne Precautions
Neisseria meningitidis (meningitis)	Tuberculosis (TB)
Group A Streptococcus	Varicella virus (chickenpox)
Rubella (German measles)	Variola virus (smallpox)
Mumps virus	Influenza A
Corynebacterium diphtheria (pharyngeal diphtheria)	Hemorrhagic Fever viruses (Ebola, Marburg, Lassa)
Bordetella pertussis (whooping cough)	Rubeola virus (measles)
Yersinia pestis (pneumonic plague)	SARS

respiratory, alimentary, genital, or urinary tracts are entered under controlled conditions without unusual contamination). As expected, compliance was best in patients with contaminated or known infected wounds.

There are three primary modes of transmission of infectious agents: contact (direct or indirect), droplet, and airborne. The most common way pathogens are transmitted is via contact. In direct contact, organisms are transmitted directly from one person to another usually via blood or bodily fluids. Contact Plus (IE: C difficile infections) requires the healthcare worker to both wash their hands and use ABHR. Droplet transmission occurs when the source coughs or sneezes and usually requires relatively close contact for the other person to become infected as droplets (large particle, >5 mm) do not remain suspended in the air for greater than three feet. Airborne transmission occurs when small particle droplets (<5 mm) are disseminated into the air, can remain there for longer periods of time, and have the ability to travel further as compared to large particles. Patients with known or suspected airborne infections should be placed in negative pressure rooms. Healthcare workers are required to wear N95 masks when they are caring for a patient with tuberculosis (Table 80.5).

## Postoperative Management of Patients Undergoing Transcatheter Aortic Valve Replacement and Transcatheter Mitral Valve Repair

Transcatheter aortic valve implantation (TAVI) was first described in 2002 and was touted as a less invasive surgical option in those with severe aortic stenosis when compared to the classic approach of an aortic valve replacement. In brief, this procedure involves the deployment of a prosthetic valve within the native, stenotic aortic valve via a catheter that is inserted into the femoral, iliac, or subclavian artery. Classically, these patients have been admitted to an ICU postoperatively; however, as the volume of these patients increases and with continued advances in surgical technique, many patients are now extubated in the operating room and have ICU lengths of stay less than 24 hours

**TABLE 80.6** Massachusetts General Hospital's Indications for Admission to the Intensive Care Unit After Transcatheter Aortic Valve Implantation

Preoperative	Intraoperative
Transapical approach	Expected postoperative intubation
Transaortic approach	Unexpected placement of a PA line
Need for preoperative hemodynamic support	Hemodynamic instability
Emergency case	Conditions requiring close monitoring (pericardial fluid, aortic injury)
Pulmonary artery catheter needed postoperative	Ischemia
Preoperative significant delirium	Significant arrhythmia
Significant pulmonary hypertension	Suspected complete heart block without adequate safe pacing
High-grade coronary artery disease	

PA, Pulmonary artery.

(Table 80.6).<sup>188</sup> Given the ever-expanding need for ICU beds, some of these patients are now brought to the PACU to recover. We have recently developed a pathway at MGH designed for specific patients to recover in the PACU, instead of going to the cardiac surgical ICU (SICU). Currently, we are relatively selective with regard to the specific patients we recover in the PACU and those who will be admitted to the ICU postoperatively.

Patients who undergo TAVIs are typically older and have a significant number of comorbidities, including coronary artery, peripheral vascular, and/or cerebrovascular disease, as well as COPD and pulmonary hypertension.<sup>189,190</sup> For the purpose of this chapter, only the immediate postoperative issues that are most commonly encountered in the PACU will be described. For a comprehensive review of ICU care following TAVI, please see chapter 54.

As with any cardiac procedure, the postoperative period may be complicated by neurologic issues (pain, altered mental status, cerebrovascular accident), cardiac issues (hemodynamic instability, arrhythmias, ischemia), and vascular access issues (bleeding). The average age at MGH of patients who undergo TAVI is 82, and the average age was 83 in the PARTNER trial.<sup>189</sup> POD is a well-known complication in older individuals undergoing cardiac surgery<sup>188</sup> and POD is associated with increased ICU and hospital length of stay, as well as increased mortality. Preventative measures to help reduce delirium, such as frequent reorientation, natural light, minimizing lines and tubes, and promoting a normal sleep-wake cycle should be utilized as often as possible. ICU stay is an independent risk factor for delirium, and simply bypassing the ICU via recovering in the PACU and discharging the patient to the floor may help decrease the incidence of delirium in this patient population. If necessary, the use of antipsychotics may be used to treat delirium, however many are associated with QT prolongation which can predispose this already fragile patient population to arrhythmias. Dexmedetomidine may be used to prevent delirium, however its associated hypotension and bradycardia may require intervention with regard to vasopressor support. When managing postoperative pain, every attempt to minimize narcotics should be undertaken, as narcotics are associated with increased delirium in the elderly. At MGH with TAVIs via the femoral route, we have found that patients do not often complain of severe pain and are easily managed with acetaminophen

and occasional low-dose fentanyl. These patients also require close monitoring—hence monitoring in the PACU for mental status changes with frequent performance of neurological exams, as the risk of stroke is the highest within the first 24 hours post-TAVI neurological event should be immediately evaluated.<sup>191,192</sup> These embolic events are most likely embolic secondary to the nature of the procedure and likelihood for embolization of calcium and microthrombi.

After undergoing a TAVI, the ejection fraction and cardiac output will increase. These changes are generally well tolerated. Pacing wires are used intraoperatively to allow for rapid ventricular pacing during valve deployment. These wires may be left in postoperatively in patients who either go into complete heart block and have not had a permanent pacemaker (PPM) placed intraoperatively. The PARTNER trial demonstrated that patients who undergo TAVI are more likely to require PPM placement than those who undergo surgical aortic valve replacement.<sup>193,194</sup> New-onset atrial fibrillation is also a common occurrence post-TAVI, however most patients are not anticoagulated given they will be started on dual antiplatelet therapy and the known association with increased risk of bleeding and even death.<sup>195,196</sup>

Vascular access site complications are a familiar occurrence following TAVI and can include retroperitoneal hemorrhage, arterial dissection, or pseudoaneurysm formation. Removal of arterial sheaths requires proper technique and includes the application of pressure at the insertion site for an appropriate amount of time.<sup>188</sup>

The first procedure involving transcatheter mitral valve repair (with the MitraClip) was performed in 2003. Mitra-Clips are a minimally invasive alternative to open valvular surgery in those who suffer from mitral regurgitation. The number of these procedures performed at MGH is less than the patients who undergo TAVI, however, within the last year we have started to recover these patients in the PACU as well. Postoperative complications to be aware of are similar to TAVIs. Bleeding is one of the most common adverse events<sup>197,198</sup> and ample pressure must be applied when the femoral venous catheter is removed. These patients commonly have atrial fibrillation, necessitating anticoagulation therapy, which only serves to further amplify the risk of bleeding, and not only from the vascular access site (i.e., GI hemorrhage). Patients who are not on anticoagulation therapy will typically receive dual antiplatelet therapy for one month postprocedure.<sup>199</sup> Fortunately, pericardial tamponade remains a rare occurrence, as does the risk of clip migration and partial clip detachment.<sup>197,198</sup>

It appears as though patients who undergo both TAVI and MitraClip procedures can recover in the PACU. Caregivers must be aware of, and remain mindful of, potential procedural complications.

## Immediate Postoperative Care of Craniotomies

In many institutions, it is the standard of care to admit patients to the neurosurgical intensive care unit (NICU) after any type of craniotomy. However, it has never been shown that this improves patients' outcomes and lately

several authors have questioned this approach. The number of NICU beds is limited and certain patients may not require this elevated level of acuity, such as those who undergo minor craniotomies.<sup>200</sup> Instead, the patients are admitted to the PACU and after they meet discharge criteria, are transferred to a lower acuity ward (neurosurgical transitional care unit [NTCU]). This approach may decrease the average hospitalization length of these patients and also provide substantial cost savings.<sup>201</sup> The goal is to reduce the demand for NICU beds and allocate resources more effectively to those for whom they are appropriate.

This is an evolving issue and obviously local conditions and policies have to be taken into account. First and foremost, the neurosurgeons have to agree to have their patients on this pathway. Furthermore, clear criteria for patients to get on this pathway have to be developed. Currently, at University of California, San Francisco (UCSF), we use a "Safe Transition Pathway" where we apply several criteria to determine whether or not a patient can safely bypass the ICU. Besides taking type of surgery, patient's age, comorbidities (especially those that would warrant postoperative ICU level of care), the duration of the procedure, and the estimated blood loss (EBL) during surgery into account,<sup>202</sup> we also only consider tumors below a certain size eligible for our pathway at UCSF. Furthermore, in order to remain on this pathway, no adverse intraoperative events should occur and the patient should have had an uneventful routine intubation and extubation.<sup>203</sup> There should not be any concerns regarding bypassing the NICU from the surgical and anesthesia teams during the debriefing at the end of surgery.

Patients on this pathway need some closer attention in the PACU. During the sign-out, the baseline neurologic examination prior to surgery should be conveyed to the PACU team (e.g., motor function, any deficits, patient conversant), as well as anticipated or expected deficits given the location of the procedure. Explicit hemodynamic goals should be clarified, especially upper limit for SBP or MAP, since even minor bleeding can have devastating consequences. Drugs to treat postoperative hypertension are either labetalol or a nicardipine infusion, since these medications do not increase cerebral vasodilation. A pupillary exam should be performed upon arrival in PACU, with the goal to rule out significant anisocoria or a unilateral, fixed, dilated pupil. Bilateral miosis is not uncommon and may be attributed to intra- and postoperative opioid administration. During the PACU stay, the head of the bed is typically elevated to promote cerebral venous drainage. Significant neck manipulation should be limited, since this can impair venous drainage. Airway obstruction and apnea should be avoided, since an increase in PaCO<sub>2</sub> will cause cerebral vasodilation and increase the intracerebral pressure (ICP). For the same reason oxygenation should be maintained, since hypoxemia will also increase the ICP. Coughing and bucking is best avoided, too, since they can also cause acute elevation of the ICP.

Common issues that can arise in the PACU in this patient population include altered mental status, which warrants frequent reassessment and examination, especially for any motor deficits. Seizures can be observed even in previously healthy patients without a history of epilepsy, since the

surgical manipulation of the brain and dura are highly irritating and do increase the risk of these occurring. The clinician's primary focus should be on terminating the seizures with IV benzodiazepines (lorazepam, midazolam) and maintaining a patent airway. Endotracheal intubation should be considered if protection of the airway in the postictal state is not possible in order to avoid hypercarbia and hypoxia. This would obviously require the patient to be transferred to the NICU. Nonsurgical causes for a seizure (e.g., hypoglycemia or electrolyte imbalance) should always be considered and ruled out. In terms of postoperative pain, headaches and neck pain are not uncommon after craniotomies, although the pain is usually not severe. Acetaminophen and low-dose opioids should be the first choice of analgesics. NSAIDs should be used either with caution or not at all in the acute postoperative setting, since they can cause intracerebral bleeding. The primary surgical team should always be consulted before the administration of any NSAIDs. Finally, PONV can occur in this patient population as well and should be treated aggressively since retching and vomiting can cause a transient increase of the ICP.

The patients will typically stay in the PACU until the routine criteria for transfer to the NTCU are met and they will continue to be monitored and examined very closely and should have telemetry and continuous pulse oximetry ordered.

## Potentially Devastating Visual Complications

### CORNEAL ABRASIONS

Corneal abrasions (CAs) are the most common ophthalmic injury in the postoperative period with an incidence ranging from 0.17% to 44%.<sup>204</sup> Many CAs are secondary to mechanical trauma and patients often complain of blurry vision, tearing, redness, photophobia, and foreign body sensation in the eye. Corneal epithelial cells are self-regenerating, and therefore CAs tend to resolve quickly with limited treatment and long-term complications are uncommon. However, the injury is unexpected, painful, and anxiety-inducing for the patient. Statistically significant risk factors include age, general anesthesia, greater average EBL, eyes taped during surgery, prone position, Trendelenburg position, and supplemental oxygen on the way to and in the PACU.<sup>204</sup> Minor CAs do not necessarily need to be evaluated by an ophthalmologist; several institutions have developed treatment protocols in conjunction with their ophthalmology department. According to these protocols, minor CAs can usually be treated by anesthesiologists, who can diagnose them and initiate a pre-established treatment regimen. However, should the patient have any vision loss, change in visual acuity, severe or uncontrolled pain, a history of refractive eye disease, a large or complicated abrasion or a foreign body, an ophthalmology consult should immediately be initiated. If the patients receive the pre-established treatment regimen, their symptoms should be resolved by the next morning, which can be confirmed with a follow-up phone call; otherwise they should be evaluated by an ophthalmologist.<sup>204,205</sup>

### POSTOPERATIVE VISION LOSS

Postoperative vision loss (POVL) is a rare but devastating complication after anesthesia. The etiology is multifactorial (e.g., CA, ischemic optic neuropathy [ION], cerebral vision loss, central retinal artery occlusion, and several other less common causes) and POVL can occur after any surgical procedure. However, there seems to be an increased incidence after spinal fusions and cardiac surgeries. ION is the most common cause of permanent POVL and accounts for 89% of POVL following prone spine surgeries.<sup>206</sup> The incidence of ION has decreased by over 50% from 1.63/10,000 (1998–2000) to 0.6/10,000 (2010–2012).<sup>207</sup> Risk factors for ION have been identified and include: male gender, obesity, use of Wilson frame, long surgery/anesthesia (>6.5 hours), high EBL (>45% of estimated blood volume), and lower percent colloid administration.<sup>208,209</sup> If POVL is suspected, immediate ophthalmologic consultation should be sought. However, the long-term outcome of this complication is unfortunately usually poor.<sup>210</sup>

## Future Considerations

### INTENSIVE CARE

In recent years, the demand for ICU beds has increased significantly within the United States and Europe. Because the PACU possesses the equipment and expertise to monitor, ventilate, and resuscitate patients recovering from general anesthesia, it has become the logical choice to provide care for critically ill patients for whom ICU beds are not available.<sup>211</sup> Although it is now common to care for critically ill patients in the PACU, the maintenance of quality patient care continues to challenge hospital administrators and staff.<sup>212</sup>

One obstacle to efficient ICU care in the PACU is the diversity of physician coverage required. Whereas the proximity of the operating room and the patient population recovering from anesthesia dictate that an anesthesiologist be the responsible physician for the majority of patients in the unit, nonsurgical ICU patients often require physician coverage by specialists who are unfamiliar with the unit and whose practices are located in distant areas of the hospital. As a result, PACU nurses must identify and contact physicians with whom they rarely interact.

Physician coverage (who will be primarily responsible for patient care—internist, anesthesiologist, or surgeon), privacy for family visitation (lack of space in a traditionally open unit), infection control (the proximity of patient beds and rapid turnover of patients), and nursing competencies (ongoing ICU training of staff) are some of the challenges facing the PACU today.<sup>213</sup> In a study of 400 ICU overflow patients admitted to the PACU in the United Kingdom, Ziser and colleagues identified insufficient medical and nursing coverage, inadequate communications, and visiting facilities for patient's families as the most significant problems facing the unit. The ICU patients in this study were on average 53 years of age with a mean length of stay of 12.9 hours. Seventy percent were mechanically ventilated,

77.8% required invasive monitoring, and 4.5% died in the PACU while awaiting placement in the ICU. The busiest hours of admission were 1 am to 11 am.<sup>214</sup>

In an effort to ensure the quality of patient care in the PACU, the professional societies responsible for the delivery of care in the unit have collaborated to develop standards for the care of ICU overflow patients. The "Joint Position Statement on ICU Overflow Patients" issued in 2000 is the result of this collaboration. It specifically requires that PACU staffing meet the nursing staffing ratios and competencies required in the critical care units.<sup>215</sup>

The Joint Position Statement reproduced here recommends that the following criteria be met:

- It must be recognized that the primary responsibility for Phase 1 PACU is to provide the optimal standard of care to the postanesthesia patient and to effectively maintain the surgery schedule.
- Appropriate staffing requirements should be met to maintain safe, competent nursing care of the postanesthesia patient as well as the ICU patient. Staffing criteria for the ICU patient should be consistent with ICU guidelines and based on individual acuity and needs.
- Phase 1 PACUs are by their nature critical care units and as such should meet the competencies required for the care of the critically ill patient. These competencies should include, but are not limited to, ventilator management, hemodynamic monitoring, and medication administration, as appropriate to their patient population.
- Management should develop and implement a comprehensive resource utilization plan with ongoing assessment that supports the staffing needs for both the PACU and ICU patients when the need for overflow admission arises.
- Management should have a multidisciplinary plan to address appropriate utilization of ICU beds. Admission and discharge criteria should be utilized to evaluate the necessity for critical care and to determine the priority of admission.

In addition to increasing the acuity of patient care in the PACU, the shortage of ICU beds has encouraged the de-escalation of care in selected patient populations. Postoperative patients who were historically admitted directly to the ICU from the operating room for intensive or specialized monitoring have had successful recovery by routine postoperative care in the PACU. Examples include postoperative craniotomy,<sup>216</sup> liver transplantation,<sup>217,218</sup> and cardiac surgery patients. The neurosurgical group at the University of Florida has shown that uncomplicated craniotomy patients can be safely cared for in the PACU at a significant savings of hospital-days and cost without increased morbidity or mortality.<sup>187</sup> Likewise, the trend to early extubation of liver transplant patients in the operating room has led to the successful uncomplicated recovery of these patients in the PACU. Finally, in an effort to protect ICU bed availability and reduce the number of cardiac surgery cancellations, a group in Melbourne established a cardiac surgery recovery unit within the PACU.<sup>219</sup> Each of these examples requires adequate space and specialized nursing skills to be successful.

## OUTPATIENT PROCEDURES

Finally, the PACU has responded to the economic restrictions that currently limit hospital resources by accommodating the performance of simple outpatient procedures (see Chapter 72).<sup>220</sup> The PACU is uniquely equipped to care for patients who are undergoing noninvasive and minimally invasive procedures such as electroconvulsive therapy,<sup>221,222</sup> cardioversion,<sup>223</sup> epidural blood patch,<sup>220</sup> and liver biopsy.<sup>220</sup> Ambulatory patients undergoing such procedures can be admitted directly to the PACU for the procedure and discharged to home after a brief recovery period. In order to do so, the PACU must be appropriately staffed and scheduled so as to not interfere with routine operating room scheduling and postoperative recovery. Electroconvulsive therapy is somewhat unique in that it requires general anesthesia that is delivered by an anesthesia care practitioner. Typically these are short procedures that can be scheduled before the routine operating room cases. One successful electroconvulsive therapy program schedules the procedure at 5:30 am with nurse-to-patient ratio of 2:1 and estimated PACU length of stay of 2 hours.<sup>222</sup>

## Summary

The PACU is more than a postanesthesia observation unit. It is unique in its ability to support the care of patients of all ages and in every stage of illness. Since its inception more than 50 years ago, the PACU has proved to be an exceptionally adaptable unit that is equipped to meet the demands of an evolving healthcare system.

## Acknowledgment

The editors and publisher would like to thank Drs. Daniel Sessler, Theodora Katherine Nicholau, and Christian C. Apfel for their contributions in the prior edition of this work. Their chapters have served as the foundation for the current chapter.

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ROBERT W. HURLEY, NABIL M. ELKASSABANY, and  
CHRISTOPHER L. WU

## KEY POINTS

- The process of nociception is a dynamic process (i.e., neuroplasticity) with multiple points of modulation. Persistent noxious input may result in relatively rapid neuronal sensitization and possibly persistent pain.
- Postoperative pain, especially when poorly controlled, results in harmful acute effects (i.e., adverse physiologic responses) and chronic effects (i.e., delayed long-term recovery and chronic pain).
- By preventing central sensitization, preventative analgesia may reduce acute and chronic pain. Although studies overwhelmingly support the concept of preemptive analgesia, the evidence from clinical trials is equivocal, mostly because of methodological issues.
- Multimodal analgesia entails use of multiple classes of analgesic drugs (acetaminophen, gabapentinoids, nonsteroidal antiinflammatory drugs [NSAIDs], ketamine, and others) to act on different receptors along the pain pathway. Different drugs act synergistically to enhance analgesia and reduce side effects resulting from use of an individual class of drugs. Use of multimodal analgesia is recommended whenever feasible.
- By allowing individual titration of analgesic drugs, use of patient-controlled analgesia (oral, subcutaneous, iontophoretic, intravenous, paravertebral, or epidural) may provide several advantages over traditional provider-administered analgesia (e.g., intramuscular or intermittent intravenous injections) in the management of postoperative pain.
- The incidence of respiratory depression from opioids is not significantly different among the various routes of administration (i.e., oral, intravenous vs. intramuscular vs. subcutaneous vs. neuraxial). Appropriate monitoring of patients receiving opioid analgesics is essential to detect those with opioid-related side effects, such as respiratory depression. When compared with systemic opioids, perioperative epidural analgesia may confer several advantages, including a facilitated return of gastrointestinal function and decrease in the incidence of pulmonary complications, coagulation-related adverse events and cardiovascular events, especially in higher-risk patients or procedures. However, the risks and benefits of epidural analgesia should be evaluated for each patient, and appropriate monitoring protocols should be used during postoperative epidural analgesia.
- Epidural analgesia is not a generic entity because different catheter locations (catheter-incision congruent vs. catheter-incision incongruent), durations of postoperative analgesia, and analgesic regimens (local anesthetics vs. opioids) may differentially affect perioperative morbidity.
- Postoperative pain management should be tailored to the needs of special populations (e.g., opioid-tolerant, pediatric, and obese patients, as well as those with obstructive sleep apnea) who may have different anatomic, physiologic, pharmacologic, or psychosocial issues.

## Fundamental Considerations

A revolution in the management of acute postoperative pain has occurred during the past four decades. Widespread recognition of the undertreatment of acute pain by clinicians, economists, and health policy experts has led to the development of a national clinical practice guideline for management of acute pain by the Agency for Healthcare Quality and Research (formerly the Agency for Health Care Policy and Research) of the U.S. Department of Health and Human Services.<sup>1</sup> This landmark document includes acknowledgment of the historical inadequacies in perioperative pain management, importance of good pain control, need for accountability for adequate provision of perioperative analgesia by health care institutions,

and a statement on the need for involvement of specialists in appropriate cases. In addition, several professional societies including American Society of Anesthesiologists (ASA),<sup>2</sup> The Joint Commission,<sup>3</sup> American Society of Regional Anesthesia and Pain Medicine, and American Pain Society<sup>4</sup> have developed clinical practice guidelines for acute pain management or provided new pain management standards. With their knowledge of and familiarity with pharmacology, various regional anesthetic techniques, and the neurobiology of nociception, anesthesiologists are prominently associated with the clinical and research advances in acute postoperative pain management. Anesthesiologists developed the concepts of acute pain services (APS) (inpatient pain services), application of evidence-based practice to acute postoperative pain, and

creation of innovative approaches to acute pain medicine (APM), all of which are a natural extension of the anesthesiologist's role as a "perioperative physician," consultant, and therapist throughout the institution, in addition to being a highly skilled expert in the operating room. Provision of effective analgesia for surgical and other medical patients is an important component of this multidimensional role. An area that is often challenging in the acute perioperative pain services (PPS) is the management of patients with acute surgical pain in addition to a baseline chronic pain. These patients are often not well served by the arbitrary distinction of "acute" versus "chronic" pain services in hospitals. Anesthesiologists are well trained to manage acute pain in the patient with concomitant chronic pain as a result of the strength of chronic pain curricula in current anesthesiology training programs. Although this chapter focuses on the patient who has acute perioperative pain, acute management of chronic pain in the hospitalized setting is discussed in [Chapter 51](#), "Management of the Patient with Chronic Pain."

## PAIN PATHWAYS AND THE NEUROBIOLOGY OF NOCICEPTION

Surgery produces tissue injury with consequent release of histamine and inflammatory mediators such as peptides (e.g., bradykinin), lipids (e.g., prostaglandins), neurotransmitters (e.g., serotonin), and neurotrophins (e.g., nerve growth factor).<sup>5</sup> Release of inflammatory mediators activates peripheral nociceptors, which initiate transduction and transmission of nociceptive information to the central nervous system (CNS) and the process of neurogenic inflammation in which release of neurotransmitters (e.g., substance P and calcitonin gene-related peptide) in the periphery induces vasodilatation and plasma extravasation.<sup>5</sup> Noxious stimuli are transduced by peripheral nociceptors and transmitted by A-delta and C nerve fibers from peripheral visceral and somatic sites to the dorsal horn of the spinal cord, where integration of peripheral nociceptive and descending modulatory input (i.e., serotonin, norepinephrine,  $\gamma$ -aminobutyric acid, enkephalin) occurs. Further transmission of nociceptive information is determined by complex modulating influences in the spinal cord. Some impulses pass to the ventral and ventrolateral horns to initiate segmental (spinal) reflex responses, which may be associated with increased skeletal muscle tone, inhibition of phrenic nerve function, or even decreased gastrointestinal motility. Others are transmitted to higher centers through the spinothalamic and spinoreticular tracts, where they induce supra-segmental and cortical responses to ultimately produce the perception of and affective component of pain.

Continuous release of inflammatory mediators in the periphery sensitizes functional nociceptors and activates dormant ones. Sensitization of peripheral nociceptors may occur and is marked by a decreased threshold for activation, increased rate of discharge with activation, and increased rate of basal (spontaneous) discharge. Intense noxious input from the periphery may also result in central sensitization ("persistent postinjury changes in the CNS that result in pain hypersensitivity")<sup>6</sup> and hyperexcitability ("exaggerated and prolonged responsiveness of neurons to normal afferent input after tissue damage").<sup>6</sup> Such noxious

input may lead to functional changes in the dorsal horn of the spinal cord and other consequences that may later cause postoperative pain to be perceived as more painful than it would otherwise have been. The neural circuitry in the dorsal horn is extremely complex, and we are just beginning to elucidate the specific role of the various neurotransmitters and receptors in the process of nociception.<sup>5</sup> However, it seems that certain receptors (e.g., N-methyl-D-aspartate [NMDA]) may be especially important for the development of chronic pain after an acute injury, although other neurotransmitters or second messenger effectors (e.g., substance P, protein kinase C) may also play important roles in spinal cord sensitization and chronic pain. Our understanding of the neurobiology of nociception has progressed from the hard-wired system proposed by Descartes in the 17th century to the current view of neuroplasticity in which dynamic integration and modulation of nociceptive transmission take place at several levels. There still are many gaps in our knowledge of the specific roles of various receptors, neurotransmitters, and molecular structures in the process of nociception.

An understanding of the neurobiology of nociception is important for appreciating the transition from acute to chronic pain. The traditional dichotomy between acute and chronic pain is arbitrary because acute pain may quickly transition into chronic pain.<sup>7</sup> Noxious stimuli can produce expression of new genes (which are the basis for neuronal sensitization) in the dorsal horn of the spinal cord within 1 hour and these changes are sufficient to alter behavior within the same timeframe.<sup>8</sup> Also, the intensity of acute postoperative pain is a significant predictor of chronic postoperative pain.<sup>9</sup> Control of perioperative pain (e.g., preventive analgesia) and the manner in which it is implemented (e.g., multimodal perioperative pain management) may be important in facilitating short- and long-term patient convalescence after surgery.

## ACUTE AND CHRONIC EFFECTS OF POSTOPERATIVE PAIN

Uncontrolled postoperative pain may produce a range of detrimental acute and chronic effects. The attenuation of perioperative pathophysiology that occurs during surgery through reduction of nociceptive input to the CNS and optimization of perioperative analgesia may decrease complications and facilitate recovery during the immediate postoperative period<sup>10</sup> and after discharge from the hospital.

### Acute Effects

The perioperative period has a variety of pathophysiologic responses that may be initiated or maintained by nociceptive input. At one time, these responses may have had a beneficial teleological purpose; however, the same response to the iatrogenic nature of modern-day surgery may be harmful. Uncontrolled perioperative pain may enhance some of these perioperative pathophysiologies and increase patient morbidity and mortality. Attenuation of postoperative pain, especially with certain types of analgesic regimens, may decrease perioperative morbidity and mortality.

Transmission of nociceptive stimuli from the periphery to the CNS results in the neuroendocrine stress response,

a combination of local inflammatory substances (e.g., cytokines, prostaglandins, leukotrienes, tumor necrosis factor- $\alpha$ ) and systemic mediators of the neuroendocrine response. The dominant neuroendocrine responses to pain involve hypothalamic-pituitary-adrenocortical and sympathoadrenal interactions. Suprasegmental reflex responses to pain result in increased sympathetic tone, increased catecholamine and catabolic hormone secretion (e.g., cortisol, adrenocorticotropic hormone, antidiuretic hormone, glucagon, aldosterone, renin, angiotensin II), and decreased secretion of anabolic hormones.<sup>11</sup> The effects include sodium and water retention and increased levels of blood glucose, free fatty acids, ketone bodies, and lactate. A hypermetabolic, catabolic state occurs as metabolism and oxygen consumption are increased and metabolic substrates are mobilized from storage depots.<sup>11</sup> The extent of the stress response is influenced by many factors, including the type of anesthesia and intensity of the surgical injury, with the extent of the stress response being proportional to the degree of surgical trauma.<sup>12</sup> The negative nitrogen balance and protein catabolism may impede convalescence; however, attenuation of the stress response and postoperative pain may facilitate and accelerate the patient's recovery postoperatively.

The neuroendocrine stress response may enhance detrimental physiologic effects in other areas of the body. The stress response is likely a factor in the postoperative development of hypercoagulability. Enhancement of coagulation (i.e., decreased levels of natural anticoagulants and increased levels of procoagulants), inhibition of fibrinolysis, and increased platelet reactivity and plasma viscosity may enhance the incidence of postoperative hypercoagulable-related events such as deep venous thrombosis, vascular graft failure, and myocardial ischemia.<sup>13</sup> The stress response may also enhance postoperative immunosuppression, the extent of which correlates with the severity of surgical injury.<sup>7</sup> Hyperglycemia from the stress response may contribute to poor wound healing and depression of immune function.

Uncontrolled postoperative pain may activate the sympathetic nervous system and thereby contribute to morbidity or mortality. Sympathetic activation may increase myocardial oxygen consumption, which may be important in the development of myocardial ischemia and infarction,<sup>13</sup> and may decrease myocardial oxygen supply through coronary vasoconstriction and attenuation of local metabolic coronary vasodilation.<sup>14</sup> Activation of the sympathetic nervous system may also delay return of postoperative gastrointestinal motility, which may develop into paralytic ileus. Although postoperative ileus is the result of a combination of inhibitory input from central and local factors,<sup>13,14</sup> an increase in sympathetic efferent activity, such as from uncontrolled pain, may decrease gastrointestinal activity and delay return of gastrointestinal function.

Nociceptors are activated after surgical trauma and may initiate several detrimental spinal reflex arcs. Postoperative respiratory function is markedly decreased, especially after upper abdominal and thoracic surgery. Spinal reflex inhibition of phrenic nerve activity is an important component of this decreased postoperative pulmonary function.<sup>13</sup> However, patients with poor postoperative pain control may breathe less deeply, have an inadequate cough, and

be more susceptible to the development of postoperative pulmonary complications.<sup>14</sup> Activation of nociceptors may also initiate spinal reflex inhibition of gastrointestinal tract function and delay return of gastrointestinal motility.<sup>13</sup>

Many detrimental postoperative pathophysiologic effects can occur in the perioperative period and can activate nociceptors and the stress response. Uncontrolled pain may activate the sympathetic nervous system, which can cause a variety of potentially harmful physiologic responses that may adversely increase morbidity and mortality. Nociceptor activation may also result in several detrimental inhibitory spinal reflexes. Control of the pathophysiologic processes associated with acute postoperative pain may attenuate the stress response, sympathetic outflow, and inhibitory spinal reflexes and contribute to improvements in morbidity, mortality, and patient-reported outcomes (e.g., health-related quality of life [HRQL], patient satisfaction).<sup>13</sup>

### Chronic Effects

Chronic persistent postsurgical pain (CPSP) is a largely unrecognized problem that may occur in 10% to 65% of postoperative patients (depending on the type of surgery), with 2% to 10% of these patients experiencing severe CPSP.<sup>15</sup> Poorly controlled acute postoperative pain is an important predictive factor in the development of CPSP.<sup>9,16</sup> The transition from acute to chronic pain occurs very quickly, and long-term behavioral and neurobiologic changes occur much sooner than was previously thought.<sup>7</sup> CPSP is relatively common after procedures such as limb amputation (30%-83%), thoracotomy (22%-67%), sternotomy (27%), breast surgery (11%-57%), and gallbladder surgery (up to 56%).<sup>9</sup> Although the severity of acute postoperative pain may be an important predictor in the development of CPSP,<sup>9</sup> a causal relationship has not been definitively established, and other factors (e.g., area of postoperative hyperalgesia) may be more important in predicting the development of CPSP.<sup>17</sup> One such factor may be the severity of the patient's preoperative pain. Patients with more intense levels of preoperative pain may also develop a degree of CNS sensitization predisposing them to the increased likelihood of higher postoperative pain and the subsequent development of chronic pain.<sup>17</sup> Thus, it is important that APS clinicians understand chronic pain conditions and involve themselves in the patient's preoperative care. The increased involvement of the APM team in preoperative anesthesia clinics or services can positively attenuate the incidence and severity of postoperative pain.

Control of acute postoperative pain may improve long-term recovery or patient-reported outcomes (e.g., quality of life). Patients whose pain is controlled in the early postoperative period (especially with the use of continuous epidural or peripheral catheter techniques) may be able to actively participate in postoperative rehabilitation, which may improve short- and long-term recovery after surgery.<sup>18</sup> Optimizing treatment of acute postoperative pain can improve HRQL.<sup>19</sup> Postoperative chronic pain that develops as a result of poor postoperative pain control may interfere with patients' activities of daily living.

### Preventive Analgesia

The older terminology of "preemptive" analgesia referred to an analgesic intervention that preceded a surgical injury

and was more effective in relieving acute postoperative pain than the same treatment following surgery. The precise definition of preemptive analgesia is one of the major controversies in this area of medicine and contributes to the question of whether preemptive analgesia is clinically relevant. Definitions of preemptive analgesia include what is administered before the surgical incision, what prevents the establishment of central sensitization resulting from incisional injury only (i.e., intraoperative period), what prevents central sensitization resulting from incisional and inflammatory injury (i.e., intraoperative and postoperative periods), or the entire perioperative period encompassing preoperative interventions, intraoperative analgesia, and postoperative pain management (i.e., preventive analgesia).<sup>6</sup> The first two definitions are relatively narrow and may contribute to the lack of a detectable effect of preemptive analgesia in clinical trials. The rationale for preemptive analgesia was based on the inhibition of the development of central sensitization. Effectively, noxious input initiated by surgical procedures induced a state of CNS hyperactivity that accentuates pain. Although a very popular and discussed theory, a single analgesic treatment (either peripheral or neuraxial) before the incision does not reduce postoperative pain behaviors beyond the expected duration of the analgesic effect.<sup>20</sup> When the block of nociceptive afferents diminishes, the surgical injury is able to reinitiate central sensitization. Clinical trials have been negative.<sup>21</sup> For these reasons, this terminology has fallen out of favor.

As stated previously, intense noxious input (e.g., postoperative pain from the periphery) can change the CNS (i.e., central sensitization) to induce “pain hypersensitivity” and hyperexcitability (i.e., exaggerated and prolonged responsiveness of neurons to normal afferent input after tissue damage). Preventive analgesia is aimed at inhibiting the development of this type of chronic pain. This definition broadly includes any regimen given at any time during the perioperative period that controls pain-induced sensitization. Central sensitization and hyperexcitability can develop after the surgical incision in a patient who has no history of preoperative pain.

In contrast, some patients may already have existing acute or chronic pain and developed central sensitization prior to the surgical incision. These patients with preexisting pain may have even more intense pain in the postoperative period. This augmentation of preexisting pain can occur in the acutely hospitalized and even in those patients in subacute or chronic outpatient settings. Preventing the establishment of altered central processing by analgesic treatment may result in short-term (e.g., reduction in postoperative pain and accelerated recovery) and long-term (e.g., reduction in chronic pain and improvement in HRQL<sup>19</sup> benefits during a patient’s convalescence). Unfortunately, many clinical studies (e.g., trials) lack clarity of study design and clear terminology of preemptive versus preventative analgesia.<sup>21,22</sup>

Timing of the intervention may not be as clinically important as other aspects of preventive analgesia (i.e., intensity and duration of the intervention). An intervention administered before the surgical incision is not preventative if it is incomplete or insufficient such that central sensitization is not prevented. Incisional and inflammatory injuries are important in initiating and maintaining central

sensitization. Confining the definition of preventative analgesia to only the intraoperative (incisional) period is not relevant or appropriate because the inflammatory response lasts well into the postoperative period and continues to maintain central sensitization.

Maximal clinical benefit is observed when there is complete multi-segmental blockade of noxious stimuli with extension of this into the postoperative period. Preventing central sensitization with intensive multimodal analgesic interventions<sup>21</sup> could theoretically reduce the intensity or even eliminate acute postoperative pain/hyperalgesia and chronic pain after surgery.<sup>9</sup>

### **Multimodal Approach to Perioperative Recovery/ Enhanced Recovery after Surgery**

The analgesic benefits of controlling postoperative pain are generally maximized when a multimodal strategy to facilitate the patient’s convalescence is implemented. Yet, postoperative pain treatment may not provide major improvements in some outcomes because it is unlikely that a unimodal intervention can be effective in addressing a complex problem such as perioperative outcomes.<sup>10,23</sup> The complex nature of nociception and mixed mechanisms of generating surgical pain are also responsible for failure of unimodal analgesia to adequately address postoperative pain.<sup>10,23</sup> Principles of a multimodal analgesia include using multiple strategies and drug classes to manage patient expectation and control postoperative pain to allow early mobilization, enteral nutrition, and to attenuate the perioperative stress response.<sup>10</sup> These strategies include: patient education, local anesthetic-based techniques (local infiltration, peripheral nerve blocks, and neuraxial analgesia),<sup>10</sup> and a combination of analgesic drugs that act via different mechanisms on different receptors within the pain transmission pathway to provide synergistic effect, superior analgesia, and physiologic benefits.

A multimodal approach to perioperative recovery to control postoperative pathophysiology and facilitate rehabilitation is an integral part of almost all enhanced recovery after surgery (ERAS) pathways and will result in accelerated recovery and decreased length of hospitalization.<sup>24</sup> One of the key components of a multimodal analgesic regimen within any ERAS pathway is the minimization of opioid use and side effects from opioids by utilizing nonopioid analgesics and techniques.<sup>25</sup> Patients undergoing major abdominal or thoracic procedures and who participate in a multimodal strategy have a reduction in hormonal and metabolic stress, preservation of total-body protein, shorter times to tracheal extubation, lower pain scores, earlier return of bowel function, and earlier fulfillment of intensive care unit discharge criteria when compared to patients receiving traditional pain management.<sup>24</sup> ERAS pathways integrate the most recent evidence from surgery, anesthesiology, nociceptive neurobiology, and pain treatment, and transforms traditional care programs into effective postoperative rehabilitation pathways.<sup>24</sup> This approach will decrease perioperative morbidity, costs of care, decrease the length of hospital stay, and improve patient satisfaction without compromising safety.<sup>26,27</sup> ERAS pathways are more common in adult surgical patients, although there is increasing interest in utilizing ERAS in pediatric patients.<sup>26</sup> Widespread implementation of these programs requires

multidisciplinary collaboration, change in the traditional principles of postoperative care, additional resources, and expansion of the traditional APS, which may be limited in the current economic climate.<sup>28</sup>

### Treatment Methods

Many options are available for the treatment of postoperative pain, including systemic (i.e., opioid and non-opioid) analgesics and regional (i.e., neuraxial and peripheral) analgesic techniques. By considering patients' preferences and making an individualized assessment of the risks and benefits of each treatment modality, the clinician can optimize the postoperative analgesic regimen for each patient. Essential aspects of postoperative monitoring of patients receiving various postoperative analgesic treatment methods are listed in **Box 81.1**.<sup>29</sup>

## Systemic Analgesic Techniques

### OPIOIDS

#### Advantages and Characteristics

Opioid analgesics are one of the cornerstone options for the treatment of postoperative pain. They generally exert their analgesic effects through  $\mu$ -receptors in the CNS, although opioids may also act at peripheral opioid receptors. A theoretical advantage of opioid analgesics is that there is no analgesic ceiling. Realistically, the analgesic efficacy of opioids is typically limited by the development of tolerance or opioid-related side effects such as nausea, vomiting, sedation, or respiratory depression. Opioids may be administered by the subcutaneous, transcutaneous, transmucosal, or intramuscular route, but the most common routes of postoperative systemic opioid analgesic administration are oral and intravenous (IV). Opioids may also be administered at specific anatomic sites such as the intrathecal or epidural space (see later sections, "Single-Dose Neuraxial Opioids" and "Continuous Epidural Analgesia").

There is wide intersubject and intrasubject variability in the relationship of opioid dose, serum concentration, and analgesic response in the treatment of postoperative pain. Serum drug concentrations may exhibit wider variability with certain routes of administration (e.g., intramuscular) than with others (e.g., IV). In general, opioids are administered parenterally (intravenously or intramuscularly) for the treatment of moderate to severe postoperative pain, in part because these routes provide a more rapid and reliable onset of analgesic action than the oral route does. Parenteral opioid administration may be necessary in patients who are unable to tolerate oral intake postoperatively. The transition from parenteral to oral administration of opioids usually occurs after the patient resumes oral intake and postoperative pain has been stabilized with parenteral opioids.

#### Intravenous Patient-Controlled Analgesia

Various factors, including the aforementioned broad interpatient and intrapatient variability in analgesic needs, variability in serum drug levels (especially with intramuscular injection), and administrative delays, may contribute to inadequate postoperative analgesia. A traditional prescribed as-needed

### BOX 81.1 Monitoring and Documentation of Postoperative Analgesia

#### Analgesic Medication\*

Medication, concentration, and dose of drug  
Settings of PCA device: demand dose, lockout interval, continuous basal infusion  
Amount of drug administered (including number of unsuccessful and successful doses)  
Limits set (e.g., 1- and 4-h limits on dose administered)  
Supplemental or breakthrough analgesics

#### Routine Monitoring

Vital signs: temperature, heart rate, blood pressure, respiratory rate, average pain score  
Pain score at rest and with activity, pain relief

#### Side Effects

Cardiovascular: hypotension, bradycardia, or tachycardia  
Respiratory status: respiratory rate, level of sedation  
Nausea and vomiting, pruritus, urinary retention

#### Neurologic Examination

Assessment of motor block or function and sensory level  
Evidence of epidural hematoma

#### Instructions Provided

Treatment of side effects  
Concurrent use of other CNS depressants  
Parameters for triggering notification of the covering physician  
Provision of contact information (24 hr/7 day per week) if problems occur  
Emergency analgesic treatment if the PCA device fails

\*Postoperative analgesia includes systemic opioids and regional analgesic techniques. This list incorporates some of the important elements of preprinted orders, documentation, and intravenous PCA and epidural analgesia daily care described in the ASA Practice Guidelines for Acute Pain Management.<sup>29</sup>

CNS, Central nervous system; PCA, patient-controlled analgesia.

(PRN) analgesic regimen probably cannot compensate for these limitations. By circumventing some of these issues, IV patient-controlled analgesia (PCA) optimizes delivery of analgesic opioids and minimizes the effects of pharmacokinetic and pharmacodynamic variability in individual patients. IV PCA is based on the premise that a negative-feedback loop exists; when pain is experienced, analgesic medication is self-administered, and when pain is reduced, there are no further demands. When the negative-feedback loop is violated, excessive sedation or respiratory depression may occur. Although some equipment-related malfunctions can occur, the PCA device itself is relatively free of problems, and most problems related to PCA use result from user or operator error.<sup>30</sup>

A PCA device can be programmed for several variables, including the demand (bolus) dose, lockout interval, and background infusion (**Table 81.1**). An optimal demand or bolus dose is integral to the efficacy of IV PCA because an insufficient demand dose may result in inadequate analgesia, whereas an excessive demand dose may result in a higher incidence of undesirable side effects such as respiratory depression.<sup>31</sup> Although the optimal demand dose is uncertain, the data available suggest that the optimal

**TABLE 81.1** Intravenous Patient-Controlled Analgesia Regimens

Drug Concentration	Size of Bolus*	Lockout Interval (min)	Continuous Infusion
<b>AGONISTS</b>			
Morphine (1 mg/mL)			
Adult	0.5-2.5 mg	5-10	—
Pediatric	0.01-0.03 mg/kg (max, 0.15 mg/kg/h)	5-10	0.01-0.03 mg/kg/h
Fentanyl (0.01 mg/mL)			
Adult	10-20 $\mu$ g	4-10	—
Pediatric	0.5-1 $\mu$ g/kg (max, 4 $\mu$ g/kg/h)	5-10	0.5-1 $\mu$ g/kg/h
Hydromorphone (0.2 mg/mL)			
Adult	0.05-0.25 mg	5-10	—
Pediatric	0.003-0.005 mg/kg (max, 0.02 mg/kg/h)	5-10	0.003-0.005 mg/kg/h
Alfentanil (0.1 mg/mL)			
Adult	0.1-0.2 mg	5-8	—
Methadone (1 mg/mL)			
Adult	0.5-2.5 mg	8-20	—
Oxymorphone (0.25 mg/mL)			
Adult	0.2-0.4 mg	8-10	—
Sufentanil (0.002 mg/mL)			
Adult	2-5 $\mu$ g	4-10	—
<b>AGONIST-ANTAGONISTS</b>			
Buprenorphine (0.03 mg/mL)	0.03-0.1 mg	8-20	—
Nalbuphine (1 mg/mL)	1-5 mg	5-15	—
Pentazocine (10 mg/mL)	5-30 mg	5-15	—

\*All doses are for adult patients unless noted otherwise. Units vary across agents for size of the bolus (mg vs. mg/kg vs. mcg vs.  $\mu$ g/kg) and continuous infusion (mg/kg/h vs.  $\mu$ g/kg/h). The anesthesiologist should proceed with titrated intravenous loading doses if necessary to establish initial analgesia. Individual patient requirements vary widely, with smaller doses typically given to elderly or compromised patients. Continuous infusions are not initially recommended for opioid-naïve adult patients.

demand dose is 1 mg for morphine and 40  $\mu$ g for fentanyl in opioid-naïve patients; however, the actual dose for fentanyl (10-20  $\mu$ g) is often less in clinical practice.<sup>30</sup> The lockout interval may also affect the analgesic efficacy of IV PCA. A lockout interval that is too long may result in inadequate analgesia and decrease the effectiveness of IV PCA. A lockout interval that is too short allows the patient to self-administer another demand dose before feeling the full analgesic effect of the previous dose and thus may contribute to an increase in medication-related side effects. In essence, the lockout interval is a safety feature of IV PCA, and although the optimal lockout interval is unknown, most intervals range from 5 to 10 minutes, depending on the medication in the PCA pump; varying the interval within this range appears to have no effect on analgesia or side effects.<sup>30</sup>

Most PCA devices allow administration of a continuous or background infusion in addition to the demand dose. Initially, routine use of a background infusion predicted certain advantages, including improved analgesia, especially during sleep; however, analgesic benefits of a background infusion have not been successful in opioid-naïve patients. A background infusion only increases the analgesic dosage used and the incidence of adverse respiratory events in the postoperative period, especially in adult subjects. Furthermore, use of a nighttime background infusion does not improve postoperative sleep patterns, analgesia, or recovery profiles.<sup>32</sup> Although routine use of continuous or background infusion as part of IV PCA in adult opioid-naïve

patients is not recommended, a background infusion in opioid-tolerant or pediatric patients may be effective (see later sections, “Opioid-Tolerant Patients” and “Pediatric Patients”) (also see Chapter 24).

When compared with traditional PRN analgesic regimens, IV PCA provides superior postoperative analgesia and improves patient satisfaction, but the presence of economic benefits is not clear.<sup>33</sup> A metaanalysis revealed that IV PCA (vs. as-needed opioids) provides significantly better analgesia and patient satisfaction; however, these patients used more opioids and had a more frequent incidence of pruritus than those treated with PRN opioids, but there was no difference in the incidence of adverse events.<sup>33</sup> With regard to economic outcomes, whether IV PCA is less expensive than traditional PRN intramuscular opioid administration is not clear because the calculations of cost are complex.

IV PCA may provide advantages when assessing other patient-related outcomes such as patient satisfaction; these outcomes have become more important as healthcare organizations use them as a measure of quality and a tool for marketing purposes. Patients usually prefer IV PCA over intravenously, intramuscularly, or subcutaneously administered PRN opioids. Greater patient satisfaction with IV PCA may be the result of superior analgesia and perceived control over the administration of analgesic medications and avoidance of disclosing pain or securing analgesic medication from nurses; however, the reasons for patient satisfaction are complex and many factors may contribute to or predict satisfaction with IV PCA. Although IV PCA use

overall creates better satisfaction, the proper assessment of patient satisfaction can be complex.<sup>34</sup>

The incidence of opioid-related adverse events from IV PCA is not different from that of PRN opioids administered intravenously, intramuscularly, or subcutaneously. The rate of respiratory depression associated with IV PCA is infrequent (approximately 1.5%) and is not more frequent than that with PRN systemic or neuraxial opioids.<sup>35</sup> Factors that may influence the frequency and intensity of respiratory depression with IV PCA include use of a background infusion, advanced age, concomitant administration of sedative or hypnotic drugs, and coexisting pulmonary disease such as obstructive sleep apnea (OSA).<sup>36</sup> IV PCA-related respiratory depression may also be caused by errors in programming or administration (i.e., operator error).<sup>37</sup>

## NON-OPIOIDS

### Nonsteroidal Antiinflammatory Agents

Nonsteroidal antiinflammatory drugs (NSAIDs) consist of a diverse group of analgesic compounds with different pharmacokinetic properties. The primary mechanism by which NSAIDs exert their analgesic effect is through inhibition of cyclooxygenase (COX) and synthesis of prostaglandins, which are important mediators of peripheral sensitization and hyperalgesia. In addition to being peripherally acting analgesics, NSAIDs can also exert their analgesic effects through inhibition of spinal COX.<sup>38</sup> The discovery of at least two COX isoforms (i.e., COX-1 is constitutive and COX-2 is inducible) with different functions (i.e., COX-1 participates in platelet aggregation, hemostasis, and gastric mucosal protection, whereas COX-2 participates in pain, inflammation, and fever) has led to the development of selective COX-2 inhibitors that differ from traditional NSAIDs, which block both COX-1 and COX-2.<sup>39</sup> The discovery of a COX-3 variant may represent a primary central mechanism by which acetaminophen and other antipyretics decrease pain and fever; however, the precise relationship between COX-3 and acetaminophen is still uncertain.<sup>40</sup>

NSAIDs given alone generally provide effective analgesia for mild to moderate pain. NSAIDs are also traditionally considered a useful adjunct to opioids for the treatment of moderate to severe pain. Yet, some quantitative, systematic reviews suggest that NSAIDs, alone or in combination with opioids, may be more beneficial than previously thought (Table 81.2 and Fig. 81.1). NSAIDs may be administered orally or parenterally and are particularly useful as components of a multimodal analgesic regimen by producing analgesia through a different mechanism from that of opioids or local anesthetics. Several meta-analyses have examined the analgesic efficacy of NSAIDs (including COX-2 inhibitors) and acetaminophen when added to IV PCA with opioids. Surprisingly and importantly, NSAIDs<sup>41,42</sup> resulted in a statistically significant (but probably not clinically meaningful) reduction in pain scores.<sup>43,44</sup> Although all regimens significantly decreased morphine consumption, only NSAIDs reduced risk for the opioid-related side effects of nausea, vomiting, and sedation.

Perioperative use of NSAIDs has several side effects, including decreased hemostasis, renal dysfunction, and gastrointestinal hemorrhage. Inhibition of COX and the formation of prostaglandins cause many of the side effects,

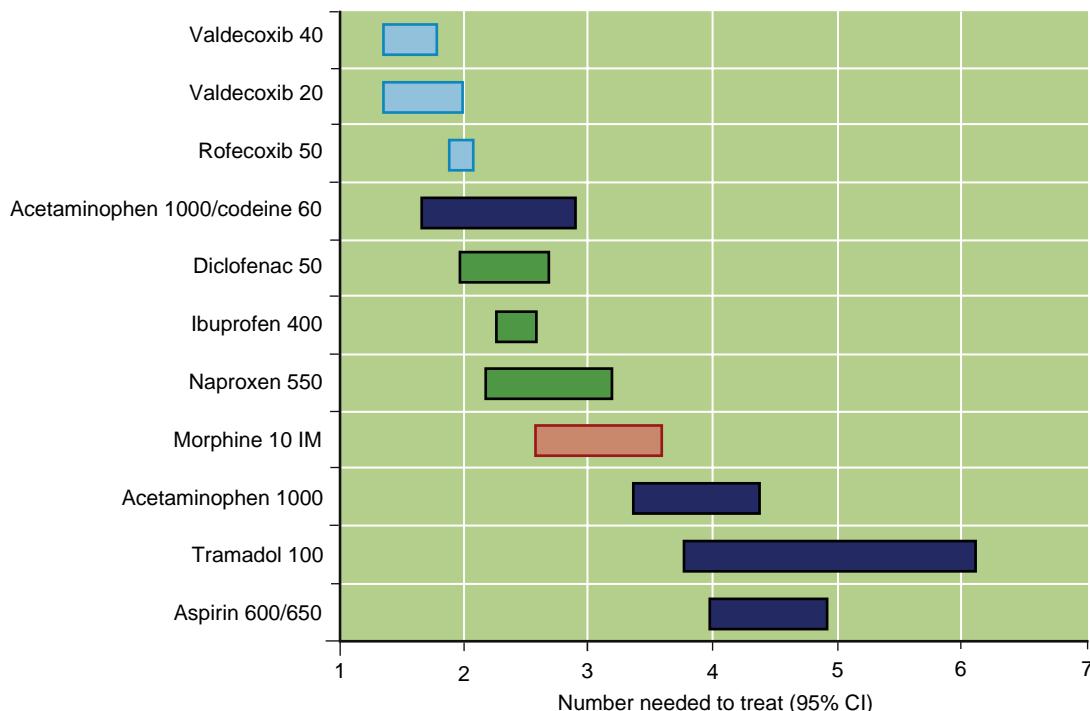
**TABLE 81.2** Relative Efficacy of Single-Dose Analgesics in Providing Greater than 50% Relief of Moderate to Severe Postoperative Pain

Drug*	Mean NNT <sup>†</sup>	95% CI
Acetaminophen (1000 mg PO)	3.8	3.4-4.4
Aspirin (600-650 mg PO)	4.4	4.0-4.9
Aspirin (1000 mg PO)	4.0	3.2-5.4
Diclofenac (50 mg PO)	2.3	2.0-2.7
Diclofenac (100 mg PO)	1.9	1.6-2.2
Ibuprofen (600 mg PO)	2.4	1.9-3.3
Ketorolac (10 mg PO)	2.6	2.3-3.1
Ketorolac (30 mg IM)	3.4	2.5-4.9
Naproxen (550 mg PO)	2.7	2.3-3.3
Celebrex (200 mg PO)	3.5	2.9-4.4
Celebrex (400mg PO)	2.1	1.8-2.5
Tramadol (100 mg PO)	4.8	3.8-6.1
Gabapentin (600 mg PO)	11	6.0-35
Codeine (60 mg) + acetaminophen (600-650 mg PO)	4.2	3.4-5.3
Oxycodone (5 mg) + acetaminophen (325 mg PO)	2.5	2.0-3.2
Codeine (60 mg PO)	16.7	11.0-48.0
Morphine (10 mg IM)	2.9	2.6-3.6
Oxycodone (15 mg PO)	2.4	1.5-4.9

\*Data obtained in part and modified from Bandolier with permission. <http://www.bandolier.org.uk/booth/painpag/Acutrev/Analgesics/lftab.html>.

<sup>†</sup>NNT in this case refers to the number of patients who must be treated to obtain greater than 50% relief of moderate to severe postoperative pain. NNT conveys statistical and clinical significance, is useful in comparing the efficacy of different interventions, and summarizes treatment effects in a clinically relevant manner. A lower mean NNT implies greater analgesic efficacy in this example. CI, confidence interval; IM, intramuscular; NNT, number needed to treat; PO, oral route.

which mediate many diverse processes throughout the body. Decreased hemostasis from NSAID use is from platelet dysfunction and inhibition of thromboxane A2 (generated by COX-1), an important mediator of platelet aggregation and vasoconstriction. Evidence of the effect of NSAIDs on perioperative bleeding is equivocal; a surveillance study of perioperative ketorolac administration did not demonstrate a significant increase in operative site bleeding. Whether NSAIDs may also have a deleterious effect on bone healing and osteogenesis is controversial. Although NSAIDs have been used following acetabular/hip fractures and hip replacement surgery to reduce heterotopic ossification, the short-term effect of NSAIDs on other skeletal tissues is less clear.<sup>45</sup> Two recent systematic reviews indicated that when examining the highest-quality studies, there was no increased risk of nonunion with NSAID exposure. Certainly, a short-term NSAID regimen can be used for treatment of post-fracture pain without significantly increasing the risk of disrupted healing.<sup>46</sup> A brief (<14 days) exposure to normal-dose NSAIDs (e.g., ketorolac <120 mg/day) was safe after spinal fusion; however, use of large-dose ketorolac



**Fig. 81.1** Number needed to treat (NNT) for at least 50% pain relief in patients with moderate to severe pain. The mean and 95% confidence interval (CI) for the NNTs are shown for several opioid and nonopioid analgesics from Table 81.2. The NNTs are derived from trials investigating the efficacy of a single dose of nonopioid analgesic versus placebo in providing more than 50% pain relief for moderate to severe postoperative pain. Numbers with drug names are doses in mg. (From Bandolier. <http://www.medicine.ox.ac.uk/bandolier/>.)

(>120 mg/day) increased the risk of nonunion, suggesting a dose-dependent effect of perioperative NSAIDs on spinal fusion healing.<sup>47</sup> Spine surgeons will more commonly err on the conservative side and refuse to have postoperative spine fusion patients receive NSAIDs.

Perioperative NSAID-induced renal dysfunction may occur in high-risk patients, such as those with hypovolemia, abnormal renal function, or abnormal serum electrolytes, because prostaglandins dilate the renal vascular beds and mediate diuretic and natriuretic renal effects. NSAIDs should not be withheld in patients with normal preoperative renal function, as euvoemic patients with normal renal function are unlikely to be affected, although NSAIDs may cause a clinically unimportant transient reduction in renal function in the early postoperative period in patients with normal preoperative renal function.<sup>48</sup> Gastrointestinal bleeding may be more likely with NSAID intake because of inhibition of COX-1, which is required for the synthesis of cytoprotective gastric mucosal prostaglandins. Bronchospasm may be induced by NSAIDs (including aspirin).<sup>49</sup> Because expression of peripheral COX-2 is increased during inflammation, selective inhibition of COX-2 could theoretically provide analgesia without the side effects associated with COX-1 inhibition. COX-2 inhibitors have a less frequent incidence of gastrointestinal complications<sup>50</sup> and exhibit minimal platelet inhibition, even when administered in supratherapeutic doses.<sup>51</sup> However, long-term use of COX-2 inhibitors has an excess cardiovascular risk such that rofecoxib was withdrawn from the market.<sup>52</sup> The cardiovascular risks of COX-2 inhibitors are heterogeneous and influenced by many factors such as the specific medication, dosage, and patient characteristics.<sup>52</sup> Issues

surrounding the perioperative use of COX-2 inhibitors are slightly different from those of longer-term use of COX-2 inhibitors. The perioperative use of potent COX-2 inhibitors resulted in a higher rate of cardiovascular events in high-risk (coronary artery bypass grafting)<sup>53</sup> but not lower-risk (major noncardiac surgery) patients. Celecoxib, a COX-2 inhibitor, has less COX-2 selectivity than other more potent COX-2 inhibitors (rofecoxib) and is still clinically available.<sup>54</sup> Nissen and associates conducted a randomized controlled trial (RCT) of 24,081 patients randomly assigned to celecoxib, naproxen, or ibuprofen and found that celecoxib was noninferior to ibuprofen or naproxen with regard to cardiovascular safety.<sup>55</sup> Liu and associates studied 10,873 patients admitted for total joint arthroplasty and concluded that perioperative use of NSAIDs was not associated with increased risk of postoperative myocardial ischemia and may reduce the hospital length of stay.<sup>55,56</sup>

Another controversial topic regarding NSAIDs is the association with postoperative bleeding. It is not surprising that several metaanalyses indicate that COX-2 inhibitors, which exhibit minimal platelet inhibition even when administered in supratherapeutic doses, are not associated with an increase in perioperative bleeding.<sup>57-59</sup> More recent metaanalyses also indicate that traditional NSAIDs (ibuprofen, ketorolac) are not associated with an increase in perioperative bleeding. Finally, some studies have been published suggesting a link between NSAIDs and anastomotic leak, but most studies are flawed or have preexisting selection bias and a metaanalysis did not demonstrate a statistically significant increase in incidence of anastomotic dehiscence with NSAIDs. Newer formulations of NSAIDs are approved for treatment of acute postoperative pain (IV ibuprofen,<sup>60</sup>

and intranasal ketorolac<sup>3</sup>). Cost of the new drugs remains to be an issue, especially in today's cost-conscious healthcare environment.<sup>61,62</sup>

## Acetaminophen

Acetaminophen has been used for several decades and is believed to have a central role of action in analgesia. It has antipyretic and antiinflammatory properties. Its mechanism of action is through activation of descending serotonergic pathways in the CNS and via the inhibition of prostaglandin synthesis.<sup>63</sup> It is used most often in conjunction with other medications as part of a multimodal analgesia protocol. Maximum recommended dose is 4 gm/day in adult patients. The US Food and Drug Administration (FDA) approved IV acetaminophen formulation for use in the United States in 2011.<sup>64</sup> Sinatra and colleagues studied the efficacy of IV acetaminophen after joint arthroplasty in a placebo-controlled study.<sup>65</sup> The study group had decreased pain scores, used fewer opioids, had a longer median time to morphine rescue compared to placebo, and were more satisfied with pain management. A metaanalysis of 865 patients enrolled in four clinical trials addressing the impact of addition of IV acetaminophen to multimodal analgesia after total hip and knee arthroplasty concluded that there was a significant decrease in pain score and opioid consumption on POD 1 to 3. Nausea and vomiting were decreased in the groups who received acetaminophen.<sup>66</sup> However, the quality of the studies included in the analysis was questioned. Peak plasma concentration is achieved faster after IV versus oral administration of acetaminophen.<sup>67</sup> Evidence to support the premise that increased bioavailability would enhance clinical efficacy is lacking. Cost effectiveness of the IV formulation and patient ability to tolerate oral intake, based on the targeted surgery, should be accounted for when considering integrating IV acetaminophen into a multimodal analgesia protocol. Data from 2013 show that the average increase in cost to hospitals adopting IV acetaminophen can be significant, based on its use.<sup>68</sup>

## Gabapentinoids

Gabapentin and pregabalin, antiepileptic drugs also used in the treatment of neuropathic pain, interact with calcium channel  $\alpha_2$ -delta ligands to inhibit calcium influx and subsequent release of excitatory neurotransmitters. However, oral pregabalin is absorbed more rapidly and has more absolute bioavailability ( $\geq 90\%$  vs.  $< 60\%$ ) than gabapentin.<sup>69</sup> Despite these differences, oral gabapentin improves the analgesic efficacy of opioids both at rest and with movement, and reduces opioid consumption and opioid-related side effects, but with a possibly increased incidence of side effects such as sedation and dizziness.<sup>70-72</sup> A metaanalysis investigating the analgesic efficacy of pregabalin for acute postoperative pain demonstrated use of pregabalin was associated with a decrease in opioid consumption and opioid-related side effects, but no difference in pain intensity.<sup>73</sup> Another meta-analysis suggested that perioperative administration of pregabalin may provide additional analgesia in

the short term but also results in an increase in side effects such as dizziness/light-headedness or visual disturbances.<sup>74</sup>

Although gabapentinoids are commonly used as part of a multimodal analgesic regimen, it should be noted that there have been recent publications questioning the analgesic benefits of gabapentinoids.<sup>75</sup> Several studies have noted that the quality of evidence for a clinically relevant benefit of gabapentinoids is low and the serious adverse events in available trials were poorly reported.<sup>76-78</sup> When examining trials with low risk of bias, gabapentinoids may actually have a minimal opioid-sparing effect but the risk of serious adverse events seems increased, as the use of gabapentin is associated with increased rates of respiratory depression among patients undergoing laparoscopic surgery.<sup>79</sup> Finally, gabapentinoids may not provide any additional analgesia for some surgical procedures including total hip arthroplasty.<sup>80</sup> The use of gabapentinoids should be considered on an individual basis after surgery.

## KETAMINE

Ketamine is traditionally recognized as an intraoperatively administered anesthetic; however, small subanesthetic dose (analgesic) ketamine can facilitate postoperative analgesia because of its NMDA-antagonistic properties, which may be important in attenuating central sensitization and opioid tolerance.<sup>81</sup> Ketamine can be administered orally, intravenously (PCA or as a continuous infusion), subcutaneously, or intramuscularly. A systematic review of perioperative ketamine use found that perioperative analgesic doses of ketamine reduce rescue analgesic requirements and pain intensity.<sup>82</sup> In addition, perioperative ketamine reduced 24-hour PCA morphine consumption and postoperative nausea or vomiting and had minimal adverse effects.<sup>82</sup> A subsequent systematic review found that IV ketamine for postoperative analgesia was an effective adjunct for postoperative analgesia, particularly in patients undergoing painful procedures such as upper abdominal, thoracic, and major orthopedic surgeries.<sup>83</sup> The administration of ketamine in postoperative pediatric patients is also associated with decreased postoperative pain intensity.<sup>84</sup> One potential concern is the possible impact of ketamine's amnestic effects on the neuropharmacologic and cognitive level of patients with use of perioperative ketamine infusions.<sup>85</sup> Although possible, these effects infrequently occur when the medication is given in analgesic doses. Ketamine has also been given epidurally and intrathecally, but racemic mixtures of ketamine are neurotoxic, and therefore the use of neuraxial racemic ketamine is strongly discouraged. Although further studies are needed to elucidate the specific parameters (e.g., dose, duration of use) for ketamine in the perioperative period, this analgesic can be considered on an individual basis as part of a multimodal approach to postoperative analgesia.

## Tramadol

Tramadol is a synthetic opioid that exhibits weak  $\mu$ -agonist activity and inhibits reuptake of serotonin and norepinephrine, although the relative degree of contribution of each modality to postoperative analgesia is not certain.<sup>86</sup> Although tramadol exerts its analgesic effects primarily through central mechanisms, it may have peripheral local

**TABLE 81.3** Properties of Neuraxial Opioids

Property	Lipophilic Opioids	Hydrophilic Opioids
Common drugs	Fentanyl, sufentanil	Morphine, hydromorphone
Onset of analgesia	Rapid onset (5-10 min)	Delayed onset (30-60 min)
Duration of analgesia*	Shorter duration (2-4 h)	Longer duration (6-24 h)
CSF spread	Minimal CSF spread	Extensive CSF spread
Site of action	Spinal ± systemic	Primarily spinal ± supraspinal
Side effects		
Nausea and vomiting	Lower incidence with lipophilic than with hydrophilic opioids	
Pruritus	Lower incidence with lipophilic than with hydrophilic opioids	
Respiratory depression	Primarily early; minimal delay	Both early (<6 h) and delayed (>6 h) possible

\*The duration of analgesia varies. CSF, Cerebrospinal fluid.

anesthetic properties and has been used as an adjunct for brachial plexus block.<sup>87</sup> Tramadol is effective in treating mild to moderate postoperative pain<sup>88</sup> and is comparable in analgesic efficacy to aspirin (650 mg), with codeine (60 mg), or ibuprofen (400 mg) (see Table 81.2 and Fig. 81.1).<sup>88</sup> The addition of acetaminophen to tramadol (vs. tramadol alone) may decrease the incidence of side effects of tramadol without reducing its analgesic efficacy.<sup>89</sup> Use of tramadol in IV PCA results in similar pain scores when compared with that from IV PCA opioids; however, the side effect profile is different between the two groups (i.e., a more frequent incidence of postoperative nausea/vomiting but lower pruritus with tramadol).<sup>90</sup> Advantages of tramadol for postoperative analgesia include a relative lack of respiratory depression, major organ toxicity, depression of gastrointestinal motility, and a theoretically lower potential for abuse.<sup>86</sup> Common side effects (overall incidence of 1.6%-6.1%) include dizziness, drowsiness, sweating, nausea, vomiting, dry mouth, and headache.<sup>88</sup> Tramadol should be used with caution in patients with seizures or increased intracranial pressure and is contraindicated in those taking monoamine oxidase inhibitors.<sup>88</sup>

### Regional Analgesic Techniques

A variety of neuraxial (primarily epidural) and peripheral regional analgesic techniques may be used for the effective treatment of postoperative pain. In general, the analgesia provided by epidural and peripheral techniques (particularly when local anesthetics are used) is site-specific and superior to that with systemic opioids, and use of these techniques may even reduce morbidity and mortality.<sup>13</sup> However, as with all approaches, the risks and benefits should be compared, especially regarding the controversies about use of these techniques in the presence of various anticoagulants.

### Single-Dose Neuraxial Opioids

Administration of a single dose of opioid may be efficacious as a sole or adjuvant analgesic drug when administered intrathecally or epidurally. One of the most important factors in determining the clinical pharmacology for a specific opioid is its degree of lipophilicity (vs. hydrophilicity) (Table 81.3). Once they have reached the cerebrospinal fluid (CSF) through direct intrathecal injection or gradual

migration from the epidural space, hydrophilic opioids (i.e., morphine and hydromorphone) tend to remain within the CSF and produce a delayed but longer duration of analgesia, along with a generally more frequent incidence of side effects because of the cephalic or supraspinal spread of these compounds. Neuraxial administration of lipophilic opioids, such as fentanyl and sufentanil, provides a rapid onset of analgesia, and their rapid clearance from CSF may limit cephalic spread and the development of certain side effects such as delayed respiratory depression. The site of analgesic action for hydrophilic opioids is overwhelmingly spinal, but the primary site of action (spinal vs. systemic) for single-dose neuraxial lipophilic opioids is not as certain.

The differences in pharmacokinetics between lipophilic and hydrophilic opioids may influence the choice of opioid aiming to optimize analgesia and minimize side effects for a particular clinical situation. Single-dose intrathecal administration of a lipophilic opioid may be useful in situations (e.g., ambulatory surgical patients) in which rapid analgesic onset (minutes) is combined with a moderate duration of action (<4 hours). Single-dose hydrophilic opioid administration provides effective postoperative analgesia and may be useful in patients monitored on an inpatient basis, for whom a longer duration of analgesia would be beneficial.

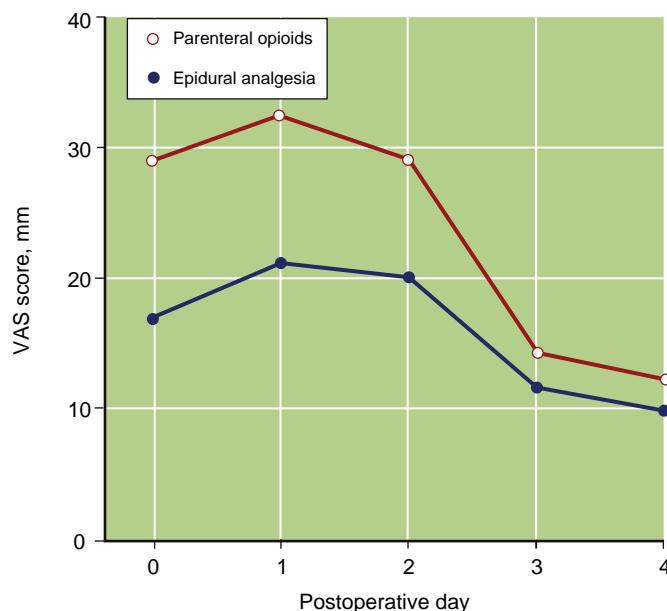
Single-dose epidural administration of lipophilic and hydrophilic opioids is used to provide postoperative analgesia, with considerations generally similar to those discussed for single-dose intrathecal administration of opioids. A single bolus of epidural fentanyl may be administered to provide rapid postoperative analgesia; however, diluting the epidural dose of fentanyl (typically 50-100 µg) in at least 10 mL of preservative-free normal saline will decrease the onset and prolong the duration of analgesia, possibly as a result of an increase in initial spread and diffusion of the lipophilic opioid. Single-dose epidural morphine is effective for postoperative analgesia and use of a single-dose hydrophilic opioid may be especially helpful in providing postoperative epidural analgesia when the epidural catheter's location is not congruent with the surgical incision (e.g., lumbar epidural catheter for thoracic surgery). Smaller doses of epidural morphine may be required for elderly patients and thoracic catheter sites. Commonly used dosages for intrathecal and epidural administration of neuraxial opioids are provided in Table 81.4.

**TABLE 81.4** Dosing of Neuraxial Opioids

Drug	Intrathecal or Subarachnoid Single Dose	Epidural Single Dose	Epidural Continuous Infusion
Fentanyl	5-25 µg	50-100 µg	25-100 µg/h
Sufentanil	2-10 µg	10-50 µg	10-20 µg/h
Alfentanil	—	0.5-1 mg	0.2 mg/h
Morphine	0.1-0.3 mg	1-5 mg	0.1-1 mg/h
Hydromorphone	—	0.5-1 mg	0.1-0.2 mg/h
Extended-release morphine*	Not recommended	5-15 mg	Not recommended

\*See package insert for details on dosage and administration.

Doses are based on the use of a neuraxial opioid alone. No continuous intrathecal or subarachnoid infusions are provided. Lower doses may be effective when administered to the elderly or when injected in the cervical or thoracic region. Units vary across agents for single dose (mg vs. µg) and continuous infusion (mg/h vs. µg/h).



No. of patient observations

Parenteral opioids	1104	2635	1496	794	536
Epidural analgesia	1010	2618	1527	822	566

**Fig. 81.2** Mean and standard deviation of visual analog pain scores (y axis) for both epidural analgesia (represented by dark blue circles) and parenteral opioids (represented by open red circles) for each postoperative day (x axis) up to the fourth day after surgery. (From Block BM, Liu SS, Rowlingson AJ, et al. Efficacy of postoperative epidural analgesia: a meta-analysis. *JAMA*. 2003;290:2455-2463, with permission.)

## Continuous Epidural Analgesia

Analgesia delivered through an indwelling epidural catheter is a safe and effective method for management of acute postoperative pain. Postoperative epidural analgesia can provide analgesia superior to that of systemic opioids (Fig. 81.2).<sup>91,92</sup> Of note, however, epidural analgesia is not a generic term but incorporates a wide range of options, including the choice and dose of analgesic drugs, location of catheter placement, and onset and duration of perioperative use.<sup>93</sup> Although this section focuses on the postoperative management of epidural analgesia, intraoperative use of the epidural catheter as part of a combined epidural-general anesthetic technique results in less pain and faster patient recovery immediately after surgery than general anesthesia followed by systemic opioids does. Each of these

options may affect the quality of postoperative analgesia, patient-reported outcomes, and even rates of morbidity and mortality.

### Analgesic Drugs

**Local Anesthetics.** Epidural infusion of local anesthetic alone may be used for postoperative analgesia, but in general it is not as effective in controlling pain as local anesthetic-opioid epidural analgesic combinations are.<sup>91,92</sup> The precise location of action of local anesthetics in the epidural space is not clear, and potential sites include the spinal nerve roots, dorsal root ganglion, or spinal cord itself.<sup>94</sup> Epidural infusion of local anesthetic alone may be warranted for postoperative analgesia in an attempt to avoid opioid-related side effects; however, the sole use of local anesthetics is less

**TABLE 81.5** Recommended Catheter Insertion Sites for Surgical Procedures

Location of Incision	Examples of Surgical Procedures	Congruent Epidural Catheter Placement
Thoracic	Lung reduction, radical mastectomy, thoracotomy, thymectomy	T4-8
Upper abdominal	Cholecystectomy, esophagectomy, gastrectomy, hepatic resection, Whipple procedure	T6-8
Middle abdominal	Cystoprostatectomy, nephrectomy	T7-10
Lower abdominal	Abdominal aortic aneurysm repair, colectomy, radical prostatectomy, total abdominal hysterectomy	T8-11
Lower extremity	Femoral-popliteal bypass, total hip or total knee replacement	L1-4

L, Lumbar level; T, thoracic level.

common than the use of a local anesthetic-opioid combination because of a significant failure rate (from regression of sensory blockade and inadequate analgesia) and relatively high incidence of motor block and hypotension.<sup>93</sup>

**Opioids for Epidural Infusion.** Opioids may be used alone for postoperative epidural infusion and do not generally cause motor block or hypotension from sympathetic blockade.<sup>93</sup> There are differences between continuous epidural infusion (CEI) of lipophilic (e.g., fentanyl, sufentanil) and hydrophilic (e.g., morphine, hydromorphone) opioids. The analgesic site of action (spinal vs. systemic) of CEI of lipophilic opioids is not clear. Although some data suggest a benefit from epidural (vs. IV) infusion of lipophilic opioids,<sup>95</sup> the overall advantage of administering CEI of lipophilic opioids alone is marginal.<sup>93</sup>

The analgesic site of action for continuous hydrophilic opioid infusion is primarily spinal. Continuous infusion of a hydrophilic opioid may be especially useful for providing postoperative analgesia when the site of catheter insertion is not congruent with the site of surgery or when side effects (e.g., hypotension, motor block) are attributed to the epidural local anesthetic. Use of a continuous infusion rather than intermittent boluses of epidural morphine may result in superior analgesia with fewer side effects. CEI of hydrophilic opioids may provide analgesia superior to that of traditional PRN administration of systemic opioids.

**Local Anesthetic-Opioid Combinations.** Use of a local anesthetic and an opioid in an epidural infusion may have advantages over infusions consisting of a local anesthetic or opioid alone. When compared with a local anesthetic or opioid alone, a local anesthetic-opioid combination provides superior postoperative analgesia (including improved dynamic pain relief), limits regression of sensory blockade, and possibly decreases the dose of local anesthetic administered, although the effect on the incidence is uncertain.<sup>93</sup> CEI of a local anesthetic-opioid combination also provides analgesia superior to that of IV PCA with opioids.<sup>91</sup> It is unclear whether the analgesic effect of the local anesthetic and opioid in epidural analgesia is additive or synergistic. The choice of local anesthetic for CEI varies. In general, bupivacaine or ropivacaine is chosen because of the differential and preferential clinical sensory blockade with minimal impairment of motor function. Concentrations used for

postoperative epidural analgesia are lower than those used for intraoperative anesthesia. The choice of opioid also varies, although many clinicians prefer a lipophilic opioid (e.g., fentanyl, sufentanil) to allow rapid titration of analgesia.<sup>93</sup> Use of a hydrophilic opioid (morphine, hydromorphone) as part of a local anesthetic-opioid epidural analgesic regimen may also provide effective postoperative analgesia. The optimal local anesthetic and opioid dose that provides the lowest pain scores with the fewest medication-related side effects is unknown and further investigation is needed to determine the optimal combinations for other types of surgical procedures with different epidural catheter insertion sites and to compare the efficacy of these optimal continuous infusions with patient-controlled epidural analgesia (PCEA).

**Adjvant Drugs.** A variety of adjuvants may be added to epidural infusions to enhance analgesia while minimizing side effects, but none has gained widespread acceptance. Two of the more studied adjuvants are clonidine and epinephrine. Clonidine mediates its analgesic effects primarily through the spinal dorsal horn  $\alpha_2$ -receptors on primary afferents and interneurons, as well as the descending noradrenergic pathway, and the epidural dose typically used ranges from 5 to 20  $\mu$ g/h. Clinical application of clonidine is limited by its side effects: hypotension, bradycardia, and sedation. Hypotension and bradycardia are both dose dependent. Epidural administration of NMDA antagonists, such as ketamine, can theoretically be useful in attenuating central sensitization and potentiating the analgesic effect of epidural opioids, but additional safety and analgesic data are needed.

### Location of Catheter Insertion

Insertion of the epidural catheter congruent to the incisional dermatome (i.e., catheter-incision-congruent analgesia) (Table 81.5) results in optimal postoperative epidural analgesia by infusing analgesics to the appropriate incisional dermatomes, providing superior analgesia, minimizing side effects (e.g., lower extremity motor block and urinary retention), and decreasing morbidity.<sup>13,93</sup> When compared with catheter-incision-congruent epidural analgesia, catheter-incision-incongruent epidural analgesia (e.g., low lumbar catheter placement for thoracic procedures) results in increased pain and early removal of the epidural catheter because of ineffective analgesia. By targeting delivery of

analgesic drugs to the appropriate dermatomes, catheter-incision-congruent epidural analgesia may result in smaller drug requirements and decreased medication-related side effects. There is a more frequent incidence of lower extremity motor block with the use of lumbar epidural catheters, and an earlier-than-anticipated termination of epidural analgesia may also result. Use of a high thoracic epidural for abdominal or thoracic surgery does not inhibit sympathetic nerve activity in the lower extremities and may result in a relatively infrequent incidence of urinary retention, thus diminishing the need for routine bladder catheterization. Placement of thoracic epidural catheters is relatively safe, and a more frequent incidence of neurologic complications is not documented with placement of a thoracic (vs. lumbar) epidural catheter. Furthermore, the benefits of epidural analgesia in decreasing morbidity in patients undergoing abdominal and thoracic surgery are seen only with thoracic (congruent), not lumbar (incongruent) epidural catheter placement.

### Side Effects of Neuraxial Analgesic Drugs

Many medication-related (opioid and local anesthetic) side effects can occur with the use of postoperative epidural analgesia, but before automatically ascribing the cause to the epidural analgesic regimen, other causes should be considered, such as small intravascular volume, bleeding, and low cardiac output leading to hypotension and cerebrovascular accident, pulmonary edema, and evolving sepsis leading to respiratory depression. Standing orders and nursing protocols for analgesic regimens, neurologic monitoring, treatment of side effects, and physician notification about critical variables should be standard for all patients receiving neuraxial and other types of postoperative analgesia (see Box 81.1).

**Hypotension.** The local anesthetics used in an epidural analgesic regimen may block sympathetic fibers and contribute to postoperative hypotension. Although the precise incidence of postoperative hypotension with postoperative epidural analgesia is uncertain, a systematic review of studies investigating postoperative analgesia found a mean (95% CI) incidence of hypotension for epidural analgesia as 5.6 (3.0%-10.2%).<sup>35</sup> Strategies to treat noncritical hypotension caused by epidural analgesia include decreasing the overall dose of local anesthetic administered (by decreasing the rate or concentration), infusing an opioid epidural alone because it is unlikely that neuraxial opioid administration would contribute to postoperative hypotension, and treating the underlying cause of the decrease in blood pressure.<sup>93</sup>

**Motor Block.** Use of local anesthetics for postoperative epidural analgesia may also contribute to lower extremity motor block in approximately 2% to 3% of patients, and this may lead to the development of pressure sores in the heels.<sup>96</sup> A metaanalysis noted a mean incidence of motor block of 3.2% with PCEA.<sup>91</sup> A lower concentration of local anesthetic and catheter-incision-congruent placement of epidural catheters for abdominal or thoracic procedures may decrease the incidence of motor block. Although motor block resolves in most cases after stopping the epidural infusion for approximately 2 hours, persistent or

increasing motor block should be evaluated promptly, and spinal hematoma, spinal abscess, and intrathecal catheter migration should be considered as part of the differential diagnosis.

**Nausea and Vomiting.** Nausea and vomiting associated with neuraxial administration of single-dose opioid occurs in up to 50% of patients, and the cumulative incidence in those receiving continuous infusions of opioid may be as high as 80%. The overall data (neuraxial opioids and/or local anesthetic combined) suggest that the incidence of postoperative vomiting is similar between epidural analgesia and systemic opioids, although female patients will exhibit a more frequent incidence regardless of analgesic modality.<sup>97</sup> The incidence of neuraxial opioid-related nausea and vomiting may be dose dependent, although a recent metaanalysis suggested that a larger dose ( $\geq 0.3$  mg) of intrathecal morphine did not increase the risk of postoperative nausea or vomiting compared to smaller dose ( $< 0.3$  mg) of intrathecal morphine.<sup>98</sup> Nausea and vomiting from neuraxial opioids may be related to the cephalad migration of opioid within the CSF to the area postrema in the medulla. Use of fentanyl alone or in combination with a local anesthetic in an epidural infusion is associated with a less frequent incidence of nausea and vomiting than infusions of morphine are. A variety of drugs have been used successfully to treat neuraxial opioid-induced nausea and vomiting, including naloxone, droperidol, metoclopramide, dexamethasone, ondansetron, and transdermal scopolamine.

**Pruritus.** Pruritus is one of the most common side effects of epidural or intrathecal administration of opioids, with an incidence of approximately 60% versus about 15% to 18% for epidural local anesthetic administration or systemic opioids.<sup>99</sup> A systematic review of studies investigating postoperative analgesia found a mean (95% CI) incidence of pruritus for epidural analgesia as 16.1 (12.8%-20%) versus 13.8 (10.7%-17.5%) for IV opioid PCA.<sup>97</sup> Although the cause of neuraxial opioid-induced pruritus is uncertain, peripheral histamine release is not the cause but may be related to central activation of an “itch center” in the medulla or activation of opioid receptors in the trigeminal nucleus or nerve roots with cephalad migration of the opioid. It is unclear whether the incidence of neuraxial opioid-related pruritus is dose dependent. Many drugs have been evaluated for the prevention and treatment of opioid-induced pruritus, which can be difficult to manage and quite bothersome for some patients. IV naloxone, naltrexone, nalbuphine, and droperidol appear to be efficacious for the pharmacologic control of opioid-induced pruritus. Serotonin receptor antagonists may also be an effective modality in the prevention of neuraxial opioid-induced pruritus. The use of epidural morphine is associated with postpartum reactivation of herpes simplex labialis.

**Respiratory Depression.** Neuraxial opioids used in appropriate doses are not associated with a more frequent incidence of respiratory depression than that seen with systemic administration of opioids. The incidence of respiratory depression with neuraxial administration of opioids is dose dependent and typically ranges from 0.1% to 0.9%. The incidence of respiratory depression, as defined by a slow

**TABLE 81.6** Patient-controlled Epidural Analgesia Regimens

Analgesic Solution*	Continuous Rate (mL/h)	Demand Dose (mL)	Lockout Interval (min)
<b>GENERAL REGIMENS</b>			
0.05% bupivacaine + 4 µg/mL fentanyl	4	2	10-20
0.0625% bupivacaine + 5 µg/mL fentanyl <sup>†</sup>	4-6	3-4	10-20
0.1% bupivacaine + 5 µg/mL fentanyl	6	2	10-20
0.2% ropivacaine + 5 µg/mL fentanyl	5	2	20
<b>THORACIC SURGERY</b>			
0.0625%-0.125% bupivacaine + 5 µg/mL fentanyl <sup>†</sup>	3-4	2-3	10-20
<b>ABDOMINAL SURGERY</b>			
0.0625% bupivacaine + 5 µg/mL fentanyl <sup>†</sup>	4-6	3-4	10-20
0.125% bupivacaine + 0.5 µg/mL sufentanil	3-5	2-3	10-20
0.1%-0.2% ropivacaine + 2 µg/mL fentanyl	3-5	2-5	10-20
<b>LOWER EXTREMITY SURGERY</b>			
0.0625%-0.125% bupivacaine + 5 µg/mL fentanyl <sup>†</sup>	4-6	3-4	10-20

\*Regimens listed are samples of local anesthetic-lipophilic opioid combinations from the literature.

<sup>†</sup>Patient-controlled epidural analgesic regimens commonly used at the Johns Hopkins Hospital.

respiratory rate, should be less than 1%.<sup>35</sup> The precise incidence of respiratory depression in actual clinical practice may be difficult to determine, as there are many criteria (e.g., respiratory rate, oxygen saturation, partial pressure of carbon dioxide, and need to administer respiratory stimulants/reversal drugs) that have been used to define respiratory depression.<sup>35</sup> Neuraxial lipophilic opioids cause less delayed respiratory depression than hydrophilic opioids, although administration of lipophilic opioids may cause early significant respiratory depression. Delayed respiratory depression is primarily associated with the cephalad spread of hydrophilic opioids, which typically occurs within 12 hours after injection of morphine. Risk factors for respiratory depression with neuraxial opioids include increasing dose, increasing age, concomitant use of systemic opioids or sedatives, possibility of prolonged or extensive surgery, and the presence of comorbid conditions (e.g., OSA). Clinical assessments, such as the respiratory rate, may not reliably predict a patient's ventilatory status or impending respiratory depression. Treatment with naloxone (and airway management if necessary) is effective in 0.1- to 0.4-mg increments; however, because its clinical duration of action is relatively short in comparison to the respiratory depressant effect of neuraxial opioids, continuous infusion of naloxone (0.5-5 µg/kg/h) may be needed.<sup>100</sup> Practice guidelines for the prevention, detection, and management of respiratory depression associated with neuraxial opioid administration have been published.<sup>101</sup>

**Urinary Retention.** Urinary retention associated with the neuraxial administration of opioids is the result of an interaction with opioid receptors in the spinal cord that decreases the detrusor muscle's strength of contraction. The incidence of urinary retention is more frequent with neuraxially administered opioids than when given systemically. Urinary retention does not depend on the opioid dose and may be treated with the use of low-dose naloxone, although at the risk of reversing the analgesic effect.

Urinary retention occurred in 23.0% of patients, with the most frequent rate in those receiving epidural analgesia.<sup>97</sup> However, the exact incidence of urinary retention seen clinically may be difficult to determine because patients who undergo major surgical procedures are often routinely catheterized.

### Patient-Controlled Epidural Analgesia

Epidural analgesia has traditionally been delivered at a fixed rate or as a CEI; however, the administration of epidural analgesia through a patient-controlled device (PCEA) has become more common. Like IV PCA, PCEA allows individualization of postoperative analgesic requirements and may have several advantages over CEI, including lower drug use and better patient satisfaction. PCEA may also provide analgesia superior to that afforded by IV PCA.<sup>91</sup>

PCEA is a relatively safe and effective technique for postoperative analgesia on routine surgical wards. Observational data from two series of over 1000 patients each reveal that more than 90% of patients with PCEA receive adequate analgesia, with a median pain score of 1 (of a possible 10) at rest and 4 with activity.<sup>102,103</sup> The incidence of side effects is 1.8% to 16.7% for pruritus, 3.8% to 14.8% for nausea, 13.2% for sedation, 4.3% to 6.8% for hypotension, 0.1% to 2% for motor block, and 0.2% to 0.3% for respiratory depression.<sup>102,103</sup> These rates are favorable and comparable to those reported with CEI.

The optimal PCEA analgesic solution and delivery parameters are unclear. Use of a continuous or background infusion in addition to the demand dose is more common with PCEA than with IV PCA and may provide analgesia superior to that of the use of a demand dose alone.<sup>104</sup> In general, most acute pain specialists have gravitated toward a variety of low-concentration local anesthetic-opioid combinations (Table 81.6) in an attempt to improve analgesia while minimizing side effects, such as motor block and respiratory depression. As for CEI, addition of an opioid to the local anesthetic can provide analgesia superior to that

of either analgesic alone. A lipophilic opioid is usually chosen because its rapid analgesic effect and shorter duration of action may be more suitable for use with PCEA.<sup>102</sup> Use of lower concentrations of a local anesthetic (e.g., bupivacaine, ropivacaine) may provide excellent analgesia without significant motor block.<sup>105</sup>

### Benefits of Epidural Analgesia

Use of perioperative epidural anesthesia and analgesia, especially with a local anesthetic-based analgesic solution, can attenuate the pathophysiologic response to surgery and may be associated with a reduction in mortality and morbidity when compared with analgesia with systemically administered opioids.<sup>13,14</sup> Metaanalysis of randomized data (141 trials enrolling 9559 subjects) found that perioperative use of neuraxial anesthesia and analgesia (vs. general anesthesia and systemic opioids) reduced overall mortality (primarily in orthopedic patients) by approximately 30%.<sup>106</sup> Use of epidural analgesia can decrease the incidence of postoperative gastrointestinal, pulmonary, and possibly cardiac complications.<sup>13,107</sup>

By inhibiting sympathetic outflow, decreasing the total opioid dose, and attenuating spinal reflex inhibition of the gastrointestinal tract, postoperative thoracic epidural analgesia can facilitate return of gastrointestinal motility without contributing to anastomotic bowel dehiscence.<sup>107,108</sup> Randomized clinical trials demonstrate that use of postoperative thoracic epidural analgesia with a local anesthetic-based analgesic solution allows earlier return of gastrointestinal function and fulfillment of discharge criteria.<sup>109</sup> When compared with those who receive epidural opioids for postoperative analgesia, patients who receive epidural local anesthetics have an earlier return of gastrointestinal motility after abdominal surgery.<sup>109</sup>

Perioperative use of epidural analgesia with a local anesthetic-based regimen in patients undergoing abdominal and thoracic surgery decreases postoperative pulmonary complications,<sup>110,111</sup> presumably by preserving postoperative pulmonary function through providing superior analgesia and thus reducing “splinting” behavior and attenuating the spinal reflex inhibition of diaphragmatic function.<sup>112</sup> A metaanalysis of 48 randomized clinical trials<sup>113</sup> and another large, randomized clinical trial<sup>114</sup> demonstrated that use of thoracic epidural analgesia with a local anesthetic-based regimen decreased the incidence of pulmonary infections and complications. However, patients who received postoperative epidural opioids, intercostal blocks, wound infiltration, or intrapleural analgesia did not have a significant decrease in the incidence of pulmonary complications.<sup>113</sup> A subsequent meta-analysis confirmed the benefits of thoracic epidural analgesia in decreasing perioperative pulmonary complications.<sup>115</sup>

Use of postoperative thoracic, but not lumbar, epidural analgesia may decrease the incidence of postoperative myocardial infarction, possibly by attenuating the stress response and hypercoagulability, improving postoperative analgesia, and providing favorable redistribution of coronary blood flow. The finding that only thoracic epidural analgesia decreases the incidence of postoperative myocardial infarction corroborates experimental data on the physiologic benefits of thoracic epidural analgesia, such as a reduction in the severity of myocardial ischemia or size of

infarction, attenuation of sympathetically mediated coronary vasoconstriction, and improvement of coronary flow to areas at risk for ischemia. The use of thoracic epidural analgesia in patients undergoing cardiac surgery decreased the risk of postoperative supraventricular arrhythmias and respiratory complications.<sup>116</sup>

Although postoperative epidural analgesia decreases postoperative gastrointestinal, pulmonary, and possibly cardiac morbidity, the benefits of postoperative epidural analgesia are not as evident in other areas, such as postoperative coagulation, cognitive dysfunction,<sup>117</sup> and immune function. While the use of *intraoperative* regional anesthesia decreases the incidence of hypercoagulable-related events (e.g., deep venous thrombosis, pulmonary embolism, vascular graft failure),<sup>106</sup> postoperative epidural analgesia does not obviously decrease the incidence of hypercoagulable-related events.

The benefits of postoperative epidural analgesia are optimized when the epidural catheter is inserted in a location corresponding to the dermatomes covered by the surgical incision (i.e., catheter-incision-congruent analgesia), which results in a smaller dose of drug administered and decreased incidence of drug-induced side effects, such as pruritus, nausea, vomiting, urinary retention, motor block, and hypotension.<sup>102</sup> When compared with catheter-incision-incongruent epidural analgesia, catheter-incision-congruent analgesia provides earlier return of gastrointestinal function, a lower incidence of myocardial infarction, and superior analgesia.<sup>112</sup> The ability of postoperative epidural analgesia to attenuate postoperative pathophysiology and improve outcomes also depends on the type of drugs used (opioids vs. local anesthetics). Maximal attenuation of perioperative pathophysiology occurs with the use of a local anesthetic-based epidural analgesic solution. The use of a local anesthetic-based (vs. opioid-based) analgesic solution is associated with earlier recovery of gastrointestinal motility after abdominal surgery<sup>109</sup> and less frequent occurrence of pulmonary complications.<sup>113</sup> Epidural analgesia is not a generic entity because different catheter locations and analgesic regimens may differentially affect perioperative morbidity.

It is unclear whether perioperative epidural analgesia may improve patient-reported outcomes.<sup>112</sup> Use of postoperative epidural analgesia may be associated with an improvement in postoperative analgesia and patient-reported outcomes such as patient satisfaction<sup>34</sup> and HRQL.<sup>19</sup> When compared with systemic opioids, epidural local anesthetics consistently provide superior analgesia.<sup>91,92</sup> Although the concept of satisfaction is complex and difficult to measure accurately, the analgesic benefits of postoperative epidural analgesia may contribute to greater patient satisfaction<sup>34</sup> and improved HRQL.<sup>19</sup>

There may be a possible link between the perioperative use of regional anesthesia/analgesia and a decrease in cancer recurrence.<sup>118</sup> There are several hypothetical reasons why the perioperative use of regional anesthesia and analgesia would be of benefit in patients undergoing cancer surgery, including attenuation of perioperative immunosuppression and decreased use of inhaled anesthetics/opioids. A regional anesthetic-induced sympathectomy should increase blood flow to the extremities with subsequent improvement in tissue oxygenation and a potential favorable local anesthetic