Hyperglycemia of Critical Illness and Pulmonary Arterial Hypertension

PSAP

By David S. Hoff, Pharm.D., FCCP

Reviewed by Kim W. Benner, Pharm.D., FASHP, BCPS; and Clarence Chant, Pharm.D., FCCP, FCSHP, BCPS

Learning Objectives

1. Distinguish the risks of hyperglycemia of critical illness (HCI) in children compared with adults.
2. Give an opinion about when a child with HCI is at increased risk of morbidity and mortality.
3. Design appropriate insulin orders for children with HCI.
4. Distinguish between the various treatments for children with pulmonary arterial hypertension (PAH) and determine when to recommend them.
5. Construct appropriate treatment plans for children with PAH.

Introduction

Of the many clinical dilemmas facing the pediatric critical care pharmacotherapist, hyperglycemia of critical illness (HCI) and pulmonary arterial hypertension (PAH) are common conditions and the subject of continuing research interest. This chapter describes these clinical conditions, characterizes recent clinical research, and outlines current treatment approaches to optimize their drug management.

Hyperglycemia of Critical Illness

Hyperglycemia affects about 20% to 86% of critically ill children, depending on the definition used for hyperglycemia and the patient subpopulation selected. Historically, hyperglycemia was considered primarily a marker of severe illness. To avoid hypoglycemia, many prescribers used insulin to limit blood glucose concentrations only when they exceeded 180–200 mg/dL. This concentration range is believed to be the renal threshold for glucose resorption and the concentration at which osmotic diuresis is more likely to occur. However, hyperglycemia is now known to be an important risk factor associated with increased morbidity and mortality in the pediatric intensive care unit (ICU).

It is not yet fully known whether hyperglycemia itself directly causes adverse outcomes in children or whether it is merely correlated with these outcomes. Many investigations chronicling the rise and fall of blood glucose in various pediatric subpopulations and its association with adverse clinical outcomes have been published. However, the various adverse clinical outcomes that may be avoided or mitigated and the range at which the blood glucose concentrations of those outcomes may be effected in children have not yet been fully explored. No consensus statements or guidelines have been published on this topic. It is important to continue studies in children with HCI to confirm similarities and define differences in this population compared with what is known in adults.

Baseline Review Resources

The goal of PSAP is to provide only the most recent (past 3–5 years) information or topics. Chapters do not provide an overall review. Suggested resources for background information on this topic include:

- Klein GW, Hojsak JM, Rapaport R. Hyperglycemia in the pediatric intensive care unit. Curr Opin Clin Nutr Metab Care 2007;10:187–92.
- Verbruggen SCAT, Joosten KFM, Castillo L, van Goudoever JB. Insulin therapy in the pediatric intensive care unit. Clin Nutr 2007;26:677–90.
- Tulloh R. Etiology, diagnosis, and pharmacologic treatment of pediatric pulmonary hypertension. Pediatr Drugs 2009;11:115–28.

Pathophysiology

Many working hypotheses for the pathophysiology of HCI in critically ill children are similar to those for HCI in critically ill adults. Although children have lower fasting blood glucose concentrations than adults, many studies published on HCI in children have shown clinical outcome patterns associated with hyperglycemia similar to those observed in adults. The following sections describe specific mechanisms using data taken from work with laboratory animals and adults with HCI and supplemented with evidence from studies of children, where available.

Insulin Resistance and Pancreatic Dysfunction

Hepatic and peripheral (i.e., muscle and adipose tissue) insulin resistance are believed to be the primary causes of hyperglycemia in critically ill adults. In adults, hepatic insulin resistance leads to unsuppressed gluconeogenesis whereas peripheral insulin resistance leads to reduced consumption of glucose by peripheral tissues. Many critically ill children also exhibit increased insulin resistance. One study found increased C-peptide concentrations in children with mild respiratory disease, indicating insulin resistance in spite of hyperglycemia. However, the investigators also found reduced C-peptide concentrations in children with more severe disease (i.e., combined respiratory and cardiovascular dysfunction), indicating that pancreatic beta-cell dysfunction also plays a role in HCI. Reduced blood insulin concentrations have been found in children with meningococcal sepsis, indicating pancreatic beta-cell dysfunction. It is reasonable to conclude from these data that both insulin resistance and pancreatic beta-cell dysfunction from a variety of causes are components of HCI in children.

Hepatic Insulin Resistance

Hepatic resistance to insulin regulatory feedback leads to the liver's inability to control increased blood glucose.

Critical illness also causes increased secretion of glucagon, cortisol, and epinephrine, leading to lipolysis in adipose tissue, proteolysis in skeletal muscle, and glycolysis in peripheral tissues. Glycerol from lipolysis, alanine from proteolysis, and lactate from glycolysis are gluconeogenic substrates that lead to increased blood glucose concentrations.

Hepatic glucokinase (hexokinase 4) causes glycolysis and glycogenesis in response to insulin and elevated blood glucose concentrations by enzymatically converting glucose to glucose-6-phosphate. Glucokinase activity is normally suppressed by elevated glucose-6-phosphate concentrations. However, during critical illness, hepatic glucokinase is not affected by exogenously administered insulin, limiting the liver's capacity to eliminate glucose from the blood.

Role of Glucose Transporters

Glucose transporter (GLUT)-1, GLUT-2, and GLUT-3 are integral membrane proteins that transport glucose into cells without insulin. They are found in hepatic, intestinal, pancreatic beta, renal tubular, endothelial, immune, erythrocyte, and neuronal cell types. During critical illness, expression of these GLUTs is increased; this, in turn, results in enhanced influx of glucose into the cells that express them, causing toxicity. In immune cells, hyperglycemia impairs the ability of leukocytes to phagocytose and generate oxidative bursts, decreases complement function, and diminishes the effectiveness of immunoglobulin function.

Glucose transporter-4 is an integral membrane protein that only transports glucose into cells in the presence of insulin. This protein is normally found in heart, skeletal muscle, and adipose tissues. In contrast to GLUT-1, -2, and -3, the activity of GLUT-4 is decreased during critical illness, reducing glucose consumption and causing hyperglycemia. Exogenous insulin administration to patients with HCI increases the expression of GLUT-4 in skeletal and adipose tissues, reducing hyperglycemia and its associated toxicity.

Unlike the unresponsiveness of hepatic glucokinase to insulin, hexokinase 2 is increased in skeletal and adipose tissues after exogenous insulin administration to patients with HCI. Hexokinase 2 metabolizes glucose by phosphorylating it to glucose-6-phosphate. This is a mechanism of action for exogenously administered insulin in patients with HCI.

Differences Between Children and Adults

Studies describing the causality of elevated blood glucose in children and adverse clinical outcomes are limited. Thus, much of the premise of glucose toxicity in the critically ill child is based on evidence in adults, which may not be appropriate in light of the many physiologic differences between children and adults. For example, death from septic shock in children occurs in

about 10% of patients and is more commonly associated with cardiac dysfunction; in adults, vasoplegic syndrome is more common, and the mortality rate is 4–5 times higher than in children. In general, the differences in the HCI rates for these conditions may affect the morbidity and mortality between adults and children.

Diabetes mellitus is less common in children than in adults. It is known that HCI-associated morbidity and mortality is more common in adults with diabetes mellitus. As a result, the effect of glucose control in children may be reduced. Further, the basal metabolic rate of nondiabetic children is 3–4 times higher than nondiabetic adults, which may point to an intrinsic difference in glucose utilization and in susceptibility to adverse outcomes associated with HCI.

Children often have diseases and comorbid conditions different from adults, which may give them either a higher or lower relative risk of mortality from HCI. For example, pediatric ICU patients more often suffer from congenital heart disease (CHD) (increased risk of HCI after surgery), bronchiolitis (no increased risk of HCI), and other respiratory dysfunction (increased risk of HCI when intubated for 48 hours or longer), whereas adults more commonly experience myocardial infarction (increased risk of HCI) and arrhythmia (increased risk of HCI). Children younger than 5 years are still undergoing critical brain development, which may make them more susceptible to neuronal damage from glucose toxicity. Alternatively, the organs and tissues of children have not been exposed to as much oxidative and hyperglycemic damage as those of adults, potentially giving children an advantage in coping with HCI. Finally, it is unknown what glucose concentration should be considered glucose toxicity in critically ill children of a given age because of the usual age-related differences in fasting glucose concentrations.

Table 1-1. Reference Values for Blood Glucose in Children

	Blood Glucose Concentration (mg/dL)
Neonates	45–90
Infants / Children /Adolescents	70–100
Severe hypoglycemia	
Neonates	Less than 45
Infants / Children / Adolescents	Less than 60
Hyperglycemia	
Fasting (upper limit)	WHO: 110
Random	ADA: 100
	Greater than 150

ADA = American Diabetes Association; WHO = World Health Organization.

Pediatric Subpopulations
Studies in the Pediatric ICU

Several definitions of hyper- and hypoglycemia exist in pediatrics (Table 1-1). Hyperglycemia affects many nondiabetic patients admitted to the pediatric ICU: peak blood glucose concentrations within 24 hours of hospital admission may be greater than 110 mg/dL (87% to 89%), 120 mg/dL (70% to 75%), 150 mg/dL (45% to 61%), and 200 mg/dL (22% to 35%).

During the past 5 years, data published on nondiabetic children critically ill from a variety of causes have produced many associations between hyperglycemia and adverse primary and secondary end points. However, not all studies controlled for disease severity and other confounding variables.

In one study, no correlation was found between mortality, ICU stay, and mechanical ventilation days after controlling for disease severity. However, the glucose cutoff of 200 mg/dL used to define hyperglycemia was criticized as being too high. In another study involving children who were mechanically ventilated for longer than 12 hours, mortality was proportional to the amount of time that blood glucose concentrations exceeded 110 mg/dL. In addition, after controlling for confounding variables, organ dysfunction and length of stay were both increased if blood glucose concentrations exceeded 180 mg/dL. Another large study randomized a mixed population of critically ill infants and children to either a low, tight glycemic target or a historical permissive glycemic target. The investigators found that use of insulin to achieve a tight glycemic target caused a reduction in mortality and other clinical end points, suggesting that insulin has a beneficial effect in a mixed population of critically ill children.

Controlled and uncontrolled studies show a strong association between hyperglycemia and negative clinical outcomes in pediatric ICU patients with a variety of conditions. Although more studies are required, glycemic control may have a role in improving clinical outcomes. In general, studies in mixed populations of critically ill children have found isolated blood glucose concentrations of 150 mg/dL or greater and blood glucose variability (i.e., oscillating from 150 mg/dL and higher to 60 mg/dL or lower) to be associated with increased mortality, hospital length of stay, and nosocomial infections. An adequately powered study to confirm or refute the potential of a type I error with respect to mortality would require about 1500 patients.

Trauma

Hyperglycemia affects more than 80% of children after severe trauma. One study evaluated the association between hyperglycemia and clinical outcomes in children with severe trauma including head trauma. Outcomes were compared between patients with a blood glucose concentration of 130 mg/dL or higher in the first

24 hours and those with a lower blood glucose concentration in the first 24 hours. Children with hyperglycemia had a longer hospital stay, more infections, and a greater need for mechanical ventilation.

In contrast to the limited data on HCI in children suffering general trauma, several studies have evaluated the association between pediatric head trauma, hyperglycemia, and outcomes. One study found no correlation between elevated blood glucose and mortality; however, this study had low statistical power, included patients with less severe head trauma (i.e., Glasgow Coma Scale score 9–10), and had a very high cutoff for defining hyperglycemia (i.e., 270 mg/dL or higher).

Another study of pediatric patients with head trauma found an odds ratio of 1.01 for mortality with hyperglycemia. Studies that have shown a direct correlation between a high blood glucose concentration upon hospital admission and mortality also found a direct correlation between a lower Glasgow Coma Scale score and increased mortality. In particular, a greater risk of mortality was found in patients with a Glasgow Coma Scale score of 8 or less and a blood glucose concentration of 200 mg/dL or higher upon hospital admission. Persistently elevated blood glucose, as determined by daily average blood glucose concentrations of 150 mg/dL or higher on all days for the first week of the hospital stay, has also been found to be an independent predictor of mortality in children with severe head trauma. More investigation must be conducted to determine whether reducing the blood glucose concentration to less than 200 mg/dL or some other concentration will reduce morbidity or mortality in this subpopulation.

Burns

Hyperglycemia is present in more than 50% of children with burn injury. Recent data have also indicated that, once burned, children exhibit a more severe and prolonged course of hypermetabolic activity, inflammatory abnormalities, and insulin resistance than after other types of injury. One study of children with severe burns covering 60% or more of their body surface area found that those with poorly controlled blood glucose had a significantly increased incidence of positive fungal blood cultures, fewer skin grafts that survived, more surgical debridement, and a higher mortality compared with a euglycemic cohort. Another study of children with burns covering 40% or more of their body surface area found that some elements of the hormonal and hepatic acute-phase response might last as long as 9 months after the initial injury. Hepatic insulin resistance can continue for 3 years after a burn injury. Insulin administration can reverse some of this, changing the hepatic acute-phase response back to a more normal process of producing constitutive proteins. Insulin administration also improves insulin sensitivity and mitochondrial oxidative capacity in these children.

Tight glycemic targets in this population have been compared with permissive hyperglycemia. Children with burns over at least 30% of their total body surface area and a blood glucose concentration greater than 140 mg/dL benefited from treatment with insulin to achieve a target blood glucose concentration of 90–120 mg/dL compared with historical controls. Children who were not treated with insulin had more urinary tract infections and considerably higher mortality.

Cardiovascular Surgery

The incidence of hyperglycemia after surgery for CHD is high; with patients exhibiting blood glucose concentrations above 125 mg/dL (about 98%), 140 mg/dL (84%), 200 mg/dL (78% to 88%), and 400 mg/dL (27%). In children who have had cardiac surgery, high and prolonged blood glucose concentrations are associated with kidney insufficiency, bacterial infections, central nervous system events, composite morbidity, need for extracorporeal membrane oxygenation, increased mortality, increased duration of mechanical ventilation, and longer ICU and hospital stays. In one model, hyperglycemia and mortality were associated with an odds ratio of 1.48. Both mortality and composite morbidity doubled after 4 days of hyperglycemia.

The effects of insulin administration for hyperglycemia after pediatric cardiac surgery have been studied. Composite morbidity was significantly higher when blood glucose was allowed to exceed 140 mg/dL. Furthermore, mortality in moderate (i.e., 140–179 mg/dL) and severe (i.e., 180 mg/dL or higher) hyperglycemia groups was 38.8% and 58.3%, respectively. Mortality rates of 6.02% and 4.69% were significantly lower in the euglycemia (i.e., 60–125 mg/dL) and permissive target groups (e.g., 90–140 mg/dL). However, the permissive target group had less hypoglycemia than the euglycemia group (17.18% vs. 31.8%). Another study found that patients maintained within a target blood glucose concentration of 80–140 mg/dL had less time on mechanical ventilation, lower rates of bloodstream infection, shorter ICU lengths of stay, and lower mortality.

Septic Shock

No study has compared glucose control versus no glucose control in children with septic shock. However, published studies have found a strong association between hyperglycemia and sepsis in most of these patients. For example, one study found that 90% of patients with meningococcal sepsis had blood glucose concentrations greater than 126 mg/dL, and 65% had blood glucose concentrations greater than 180 mg/dL. Hyperglycemia was associated with insufficient insulin production, not insulin resistance, as is more commonly reported in adults.

As in other pediatric disease states, hyperglycemia in children with septic shock correlates with mortality and adverse clinical outcomes. In one study, the highest

glucose concentration measured on admission was 262 mg/dL in non-survivors and 168 mg/dL in survivors. The mortality rate was 27.6% in patients with a peak admission blood glucose concentration less than 178 mg/dL and 71.4% in patients with a glucose concentration of 178 mg/dL or higher. Therefore, children with septic shock had an odds ratio of mortality of 2.59 if the blood glucose concentration was greater than 178 mg/dL. Patients with meningococcal sepsis and a peak blood glucose concentration greater than 126 mg/dL experienced significantly higher mortality, more severe illness, and poorer outcomes than those with euglycemia. In this same population, elevated mean blood glucose concentration in the second 24 hours after admission was associated with longer time on inotropic support, higher incidence of skin necrosis, and greater need for renal replacement therapy.

Treatment Goals

The effects of acute hypoglycemia in critically ill children are described in the literature. Severe hypoglycemia (i.e., less than 40 mg/dL) is a concern in critically ill patients because the symptoms are often masked by the patient's young age, disease state, or drugs and because the adverse clinical effects can occur precipitously and may be severe. Even a single episode of severe hypoglycemia can cause arrhythmias, coma, irreversible brain damage, and death. This concern is separate from worsened clinical outcomes of HCI associated with glucose variability of less than 60 mg/dL and 150 mg/dL or more for brief periods. Therefore, HCI protocols designed for children must not only consider blood glucose variability but also aim to eliminate severe hypoglycemic episodes.

Surveys of pediatric intensivists and nurses show considerable variability in the definitions of hyperglycemia and hypoglycemia and proper target blood glucose concentrations when using insulin for HCI. Pediatric intensivists usually use a threshold of around 150 mg/dL for hyperglycemia and 60 mg/dL for hypoglycemia. However, more clinical outcomes data from large, randomized clinical trials of children with HCI are needed to further define these glucose cutoffs.

From the data on non-neonatal, medical-surgical children in the pediatric ICU, it would be prudent to use a blood glucose of about 150 mg/dL or greater as a trigger for treatment with a standardized insulin protocol, taking care to avoid blood glucose variability. Insufficient data are available to suggest that tight glycemic targets in the ranges normal for age are superior to more permissive intermediate hyperglycemic targets. In fact, tight glycemic targets may be harmful. In adults, the Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study showed increased mortality and hypoglycemia with a tight target (81–108 mg/dL) versus an intermediate hyperglycemia target (180 mg/dL or less). In contrast, a 2001 study of adults showed a significant reduction in mortality with a tight target, but this study compared a target in the normal blood glucose range (80–110 mg/dL) with a historical permissive glycemic target (180–200 mg/dL), which at the time was usual care in that particular ICU.

Similarly, a 2008 study of glucose control in children after repair of congenital heart defects found the lowest mortality in patients maintained in a permissive hyperglycemia target range (140–179 mg/dL) compared with those who were euglycemic or severely hyperglycemic (180 mg/dL or greater), although the difference was only statistically higher for the severely hyperglycemic group. The lower mortality rate with the permissive hyperglycemia target may indicate a J-shaped association curve between blood glucose concentration and mortality, with the lower part of the curve extending into the permissive hyperglycemic range (e.g., up to 150 mg/dL) but not into significant hyperglycemia (e.g., 180 mg/dL or greater).

Data in children with head trauma suggest that a threshold of 150 mg/dL will also reduce adverse outcomes. In general, patients with trauma have better clinical outcomes with blood glucose concentrations less than 130 mg/dL. Data support an upper blood glucose concentration threshold of 140 mg/dL in children with burns covering 40% or more of their body surface area. These children may benefit by intravenous insulin initiation with a blood glucose concentration goal of 90–120 mg/dL.

Children who undergo cardiac surgery benefit from a glucose target range of 90–140 mg/dL if their blood glucose concentration is greater than 140 mg/dL. Children with sepsis have better clinical outcomes with lower peak blood glucose concentrations, but it is difficult to discern a logical target from the literature. It would be best to treat the patient with an insulin infusion if the blood glucose concentration exceeded 130 mg/dL, although the glucose threshold of 150 mg/dL recommended by the Surviving Sepsis Campaign for adults is also reasonable. No evidence-based cutoffs can be applied to children with bronchiolitis because evidence in this subpopulation does not show a correlation between hyperglycemia and poor clinical outcomes.

Quality Patient Care
Glucose Monitoring

In critically ill children at risk of HCI, blood glucose concentrations should be monitored often to identify early increases in blood glucose, precipitous declines in blood glucose with insulin therapy, and hyper- and hypoglycemic variability that may lead to poor clinical outcomes. Point-of-care blood glucose monitoring can minimize the quantity of blood needed for glucose measurements. No standard sampling frequency has been

established, but published protocols suggest venous or arterial blood samples every hour until the glucose concentration is stable and in the target range and then every 3–4 hours thereafter.

Central laboratory measurements of arterial blood provide the most accurate assessment of blood glucose concentrations. One study found about 77% clinical agreement with arterial samples measured by the central laboratory and about 70% clinical agreement with arterial samples measured by a point-of-care meter. Only about 57% clinical agreement occurred with capillary blood samples measured by a point-of-care meter. Although central laboratory data are the most accurate, point-of-care blood monitoring is still the preferred method for HCI protocols because each central laboratory measurement can take 30–60 minutes for the results to get to the bedside. This delay is too long for rapid titration of an insulin infusion for an HCI protocol, increasing the potential for glucose variability and excess hypoglycemia.

Some studies of children have successfully sampled capillary blood measurements with a subcutaneously placed glucose monitoring system. However, although the monitor detects considerably more glucose variability and provides a more rapid assessment of blood glucose, there is concern about the accuracy of the device at the lower end of the glucose target range because the lower limit of detection is 40 mg/dL.

Elements of an Appropriate Insulin Order

A quality insulin order for HCI should contain more than just the type of insulin, dose, administration route, and frequency. Because insulin is a high-risk drug, insulin orders should contain safeguards that take into consideration that the desired effect may not always occur in every patient. These order elements will increase the chances of therapeutic success and offer quick resolution in cases of therapeutic misadventure.

Regular insulin is preferred for treating HCI in children because no information is available on the use of insulin analogs for this indication. A concentration of 1 unit/mL mixed in normal saline is appropriate for continuous intravenous infusion in most critically ill children. Children with HCI are usually quite dynamic in their clinical presentation, requiring rapid titration of insulin for changing blood glucose concentrations. Therefore, subcutaneously administered insulin suspensions are inappropriate because of their slow onset of action and inability to be titrated rapidly. Continuous intravenous infusion of regular insulin is preferred over intermittent intravenous bolus injections or subcutaneous "sliding-scale" insulin administration.

Every insulin order should contain an explicitly written target range for blood glucose. The range should be evidence based and relevant to the patient's age and condition. An explicitly written target range will remove ambiguity from the therapy goal and align the staff caring

---

Box 1-1. Sample Pediatric Hypoglycemia Protocol

Event: blood glucose less than 60 mg/dL

Action steps:

1. Discontinue insulin infusion.
2. Give 25% dextrose 1 mL/kg intravenously over 10 minutes.
3. Notify the intensivist.
4. Repeat blood glucose sampling every 20 minutes until the blood glucose concentration is > 60 mg/dL.
5. Repeat dextrose dose after every blood glucose concentration that is < 60 mg/dL.
6. Do not reinitiate insulin infusion until the blood glucose concentration is > 150 mg/dL on three successive checks 20 minutes apart.

---

for the patient. A specific order should be written to discontinue the insulin infusion at a predetermined blood glucose concentration, reducing the chance that the patient will become hypoglycemic and ensuring that the insulin infusion will be discontinued at lower blood glucose concentrations.

An order should be written to infuse dextrose for a very low blood glucose concentration. A sample hypoglycemia protocol is given in Box 1-1. Documenting a clear protocol for hypoglycemia will eliminate the time needed to contact a prescriber, react to the value, and write an order for rescue dextrose. In addition, insulin orders should indicate that the prescriber should be directly contacted if the patient experiences predetermined thresholds for either low (e.g., less than 60 mg/dL) or high (e.g., greater than 300 mg/dL) blood glucose concentrations, or any significant change (e.g., greater than 100 mg/dL) in blood glucose. Insulin orders should also indicate that the prescriber should be contacted if the patient experiences any change in neurologic status. Finally, the prescriber should be directly contacted if the patient's blood glucose concentration does not achieve the target range within a specific time (e.g., 12 hours). Predetermined guidelines for prescriber involvement will bring early needed attention to patients who do not respond as expected to the insulin infusion.

Three protocols for managing HCI in children have been published. Results from the use of the Emory protocol in a mixed pediatric ICU population and a postoperative cardiac surgery population have been published. The 2009 Leuven protocol and the Rotterdam protocol enrolled critically ill infants and children with mixed disorders. The treatment arms of the Emory and Rotterdam protocols maintained blood glucose concentrations in a range that included some permissive hyperglycemia (Emory: 80–140 mg/dL; Rotterdam:

72–145 mg/dL), whereas the 2009 Leuven protocol maintained lower target glucose concentrations (infants, 50–79 mg/dL; children, 70–99 mg/dL).

There were several differences in the reported outcomes. One important difference was the incidence of hypoglycemia. The Emory protocol resulted in the lowest percentage of patients experiencing hypoglycemia: 6.7% to 10% of patients had a blood glucose measurement less than 60 mg/dL, and 0% to 4% had a blood glucose concentration less than 40 mg/dL. The Rotterdam protocol resulted in 30% of patients having at least one blood glucose concentration less than 72 mg/dL, and the 2009 Leuven protocol resulted in 24.9% and 4.9% of patients experiencing blood glucose concentrations less than 40 mg/dL and 31 mg/dL, respectively.

Institutions implementing an HCI protocol can start with a published protocol and modify it for their target population, tolerance of the risk of hypoglycemia, and target blood glucose concentration range. In addition to including the elements of a quality insulin order, the ideal glucose control protocol will be easy to use and will include regular and accurate measurements of blood glucose concentrations to ensure protocol safety and responsiveness. Moreover, this protocol will provide consistent administration of a minimal amount of dextrose calories to reduce the potential for blood glucose swings and account for dynamic changes in feeding or dextrose administration. An initial dextrose infusion rate of 0.1–0.2 g/kg/hour (1.7–3.4 mg/kg/minute) should be adequate for most children. This minimal dextrose infusion is not meant to provide sufficient calories for the patient's nutritional needs. Enteral or parenteral nutrition should also be established.

A trained staff member should follow the insulin protocol consistently and provide a continuous presence at the patient's bedside. Normally, either prescribers or nurses run these protocols, but pharmacists are also appropriate if they can provide a consistent and continuous presence at the patient's bedside. Time is an important factor to consider before launching an insulin protocol because it may require up to 2 hours/patient/day of additional time in a pediatric ICU. One investigator found that nurses spent a median of 4.72 minutes per blood work–titration cycle. This extra time presents a dilemma because protocol standardization is best completed by a small group of committed staff (i.e., the larger the staff, the greater potential for variability). The additional time required for protocol management may overwhelm the resources of a small staff. It is therefore essential that nurses be involved in protocol planning.

Complex insulin protocols that are launched without thorough nursing input have a high likelihood of failure. Common nursing barriers to implementing an HCI protocol include concern about increased time spent drawing samples, fear of hypoglycemia, fear of not remembering the schedule of frequent blood glucose checks, skepticism that the protocol will keep the patients in the target range, and skepticism that maintaining euglycemia improves patient clinical outcomes. These barriers should be addressed to ensure a successful protocol launch. Emphasis should be placed on nursing autonomy with the protocol. In-service training sessions should be conducted with all nurses who will work with the protocol. Expectations and standards around the incidence and treatment of hypoglycemia should be reviewed. Computerized alerts, flow sheets, on-call providers to handle questions, and regularly solicited nursing feedback help improve protocol decision-making. Visible reminders (e.g., printed protocol, clinical pearls cards), smart intravenous pump technology, and active double checks will help improve safety.

Each glucose control protocol should begin with criteria for the type of patient for whom the protocol will be applied. Patients with trauma, sepsis, burns over more than 40% of total body surface area, anticipated intubation longer than 48 hours, neurologic injury, or those who have had cardiovascular surgery are potential populations. Surveillance blood glucose measurements should be ordered on a regular basis (usually every 4–6 hours for the first 48 hours) to detect HCI.

The protocol should explain the method for blood glucose sampling to reduce the potential for artifact. It is best to draw glucose samples from a catheter that does not have a dextrose-containing fluid running through it. It is also important that sampling be conducted from the same site and using the same sampling protocol to avoid variability. Blood glucose concentrations can vary as much as 34% between venous, arterial, and peripheral sites when sampled from the same patient at the same time. Arterial catheters or peripheral blood samplings have the least amount of artifact. Significant hypoglycemia may result from increasing the insulin based on a blood glucose sample that is falsely elevated because it contains dextrose from an intravenous catheter. Furthermore, if hyperglycemia is detected, a blood glucose concentration should be repeated about 1 hour after the first sample to confirm the results, thus reducing the potential for initiating insulin therapy based on a temporary increase in glucose or a sample artifact.

The target range for blood glucose should be prominently displayed in the patient's medical record and at the bedside. Next, a standardized insulin dose should be ordered if the initial blood glucose concentration exceeds a predetermined threshold (e.g., 150 mg/dL). A conservative initial insulin infusion rate in children is 0.05 units/kg/hour. Blood glucose concentrations should be measured hourly until the glucose is within the target range. The insulin infusion rate should be adjusted according to the protocol to move the blood glucose concentration into the target range without causing hypoglycemia.

The Emory protocol recommends increasing the insulin dose by 50% if the blood glucose decreases by less

than 25 mg/dL but remains above the upper target limit. A 50% reduction in the insulin dose is recommended if the blood glucose decreases by more than 75 mg/dL. The Rotterdam protocol offers several choices for insulin dosage adjustment that depend on the percent change in the blood glucose concentration and the glucose concentration after the change. The 2009 Leuven protocol does not describe the mechanism for adjusting the insulin dosage. Both the Emory and Rotterdam protocols require hourly blood glucose checks until the blood glucose is within the target range for three consecutive samples; the checks can then be reduced to every 3–4 hours. The serum potassium concentration should be sampled at least every 12 hours while the patient is receiving insulin because insulin can cause hypokalemia.

Using high doses of corticosteroids administered intermittently will likely cause acute fluctuations in the blood glucose concentration. Converting the intermittent boluses of corticosteroids to a continuous infusion may reduce acute fluctuations in the blood glucose concentration. However, no specific guidance is available for adjusting insulin dosing for corticosteroid administration.

The insulin infusion should be reduced (e.g., by 25%) if the blood glucose concentration falls into the low end of the target range (e.g., 80–100 mg/dL); if it falls below the low end of the target range (e.g., less than 80 mg/dL), insulin should be discontinued. Usually, a 50% reduction in insulin dosage is made if intravenous dextrose infusions including parenteral nutrition or enteral feeding rates are reduced or if the patient is converted from parenteral to enteral nutrition. Decreases in blood glucose concentrations can occur in patients on insulin infusions when enteral feedings are temporarily discontinued for procedures, general care, or medication administration.

Cost of Glycemic Control

Considerable resources are needed to research, develop, plan, and launch an insulin protocol for HCI. Initially, a few individuals' time is needed to plan the protocol. The number of involved staff increases as they become trained on the protocol, and resources are more quickly consumed after the protocol is launched. During a 1-year study of a 58-bed adult ICU, 77,954 blood glucose concentrations were sampled, $58,500 was spent on supplies, and $182,488 was spent on nursing salaries because of workload directly related to glucose control. This example shows that a budget, a human resource management plan, and an understanding of the effect of frequent blood glucose monitoring on nursing workload should be reviewed early in planning an insulin protocol. In contrast, the authors of a different study in an adult ICU found a savings of $3,511 per patient who received insulin for HCI compared with the conventional treatment group. However, the authors did not consider staffing costs in their model because staffing conditions were unchanged by implementing the insulin protocol.

Conclusion

Hyperglycemia of critical illness is a worrisome condition. Strict glycemic targets, as in the 2001 Leuven study of adults, heralded the potential for an extraordinary opportunity to reduce mortality from HCI. A 2006 consensus development conference involving 12 health care associations called for improved inpatient glycemic control in adults. More recently, the somewhat unexpected results of the NICE-SUGAR trials of adults showed increased mortality and hypoglycemia with low, tight glucose targets compared with permissive hyperglycemia.

No guidelines for blood glucose concentration limits for HCI in children have been established. Studies of critically ill children are becoming more numerous and are increasingly using control groups and gaining in statistical power. It is hoped that this new information will clarify the uniqueness of the pediatric population and more clearly identify opportunities for applying safe and validated protocols to optimize glycemic control in the pediatric ICU.

Pediatric PAH

Pulmonary arterial hypertension is a serious and often fatal disease in children. The 1-year survival rate was 62% in the 1960s. However, after epoprostenol became available in 1995 and with advances in cardiac surgery, children with PAH can now have an improved quality of life and pulmonary hemodynamics. Mortality at 4 years after the initial diagnosis is now about 10% to 20%. Although there remains no cure, several new drugs with different mechanisms of action have become available to expand the treatment options for children with PAH.

The normal mean pulmonary arterial pressure (MPAP) in newborns within the first 2 weeks of life ranges from 17 mm Hg to 65 mm Hg. However, after 2 weeks of life, MPAP values become similar to those of older infants, children, and adults, ranging from about 12 mm Hg to 16 mm Hg. Pulmonary hypertension is defined in both children and adults as an MPAP greater than 25 mm Hg. A subset of pulmonary hypertension, PAH is further defined as a pulmonary capillary wedge pressure of 15 mm Hg or less and a pulmonary vascular resistance greater than 3 Wood units.

Clinical sequelae of PAH do not usually become clinically significant until the MPAP is at least 60 mm Hg. Cardiac catheterization is the gold standard for defining pulmonary pressure. At the time of diagnosis, a test for pulmonary artery vasoresponsiveness should be conducted with a fraction of inspired oxygen (FiO_2) of 100% and inhaled nitric oxide (NO) at a concentration of 20–40 ppm or other pulmonary vasodilator (e.g., intravenous adenosine, inhaled iloprost) to determine which patients may respond to chronic vasodilator therapy. Vasoresponsiveness is defined by the American College

of Cardiology as a reduction in MPAP by at least 10 mm Hg to an absolute MPAP of less than 40 mm Hg with normalization of cardiac output.

Symptoms of PAH can be subtle and easily overlooked without reasonable suspicion. Infants and children who should be assessed for PAH include those who have dyspnea, dizziness, or syncope on exercise, as well as those who tire easily, complain of chest pain, or have cool extremities in the absence of known heart or lung disease. Signs of right heart failure (e.g., peripheral edema, ascites, hepatomegaly) usually occur late in the disease process in children. Furthermore, PAH is classified by the World Health Organization (WHO) into four functional classes based on patient symptoms (Box 1-2).

The pathophysiologic changes in PAH are multifactorial. Early in the course of PAH, the condition presents primarily with reversible vasoconstriction of small pulmonary arterioles on exposure to exercise, hypercarbia, or hypoxia, which causes restricted pulmonary blood-flow and ventilation-perfusion mismatch. The reactive vascular endothelium expresses a decreasing amount of vasodilatory NO and vasoactive intestinal peptide and an increasing amount of the pulmonary vascular growth promoter and vasoconstrictor endothelin-1. Serotonin promotes arteriolar muscle cell mitogenesis.

As PAH progresses, enhanced vasoconstriction is caused by increased phosphodiesterase (PDE)-5 gene expression, and vasoconstriction and platelet aggregation are caused by increased thromboxane A_2. Furthermore, prostacyclin activity is reduced in patients with PAH because of reduced prostacyclin synthase activity and prostacyclin receptor expression. Prostacyclin is a protective vasodilator and inhibitor of platelet aggregation and arteriolar muscle cell growth. Later in the course of PAH, pathology is consistent with impaired endothelial cell apoptosis and local thromboses.

Left untreated, PAH leads to irreversible obstructive remodeling of the pulmonary arteries, vascular cell proliferation, thickened musculature, inflammation, and fibrosis. The result is progressively increased MPAPs,

right ventricular heart failure, and worsened PAH. Atrial septostomy or lung transplantation may be required unless the underlying cause is corrected or slowed with drug therapy. Drug therapy can slow the progression of PAH, improve quality of life, improve exercise tolerance, and reduce mortality.

Differences Between Children and Adults

Young children with PAH exhibit increased reactive pulmonary vasculature in response to exercise and hypoventilation compared with older children and adults. Similarly, pulmonary vasoresponsiveness during cardiac catheterization occurs in about 30% to 40% of children with idiopathic disease but in only 10% to 15% of adults. Medial pulmonary arteriolar hypertrophy is the only histologic feature of PAH in infants and is a prominent feature in children younger than 15 years. Older children present with a pattern of vascular lesions similar to that of adults.

Populations with PAH

Congenital heart disease is responsible for the development of PAH in about 52% of childhood cases; pulmonary disease is the cause in about 13% of cases; and the remaining cases (about 35%) have idiopathic PAH.

Congenital Heart Disease

Congenital heart disease is the most common cause of PAH in children. However, CHD has become less common because of improved early access to advanced surgical techniques to correct the heart defects that cause PAH (e.g., large ventricular septal defects, patent ductus arteriosus, large secundum atrial septal defects, transposition of the great vessels, truncus arteriosus, atrioventricular canal). Clinical symptoms of PAH secondary to heart defects are not usually seen in the newborn. As PAH progresses, signs may appear within the first year to several years of life, with considerable clinical deterioration in the teenage years.

In patients with CHD, PAH begins with elevated MPAPs secondary to the left-to-right shunting of blood. The MPAP may increase to the point where it meets or exceeds the systemic vascular resistance, causing the left-to-right shunt to stop. If detected early, elevated MPAPs can be normalized by surgical correction of the heart defect. An acute, severe form of PAH called *pulmonary hypertensive crisis* can occur after the surgical repair of heart defects. In this case, MPAPs increase rapidly, leading to respiratory failure and increased central venous pressure.

Chronically, elevated MPAPs lead to turbulent shear forces at pulmonary arterial branches and on the epithelial surface of the vascular intima. Vascular cell proliferation occurs because of the overexpression of vascular endothelial growth factor. The muscular vascular intima becomes thickened. Mechanical stress causes the expression of endothelial cell genes that cause the proliferation of endothelial cell clones, forming plexiform lesions. Finally, advanced PAH is associated with impaired antiapoptotic signaling, decreased endothelial cell apoptosis, and proliferation of inflammatory cells into arterial structures.

Sickle Cell Disease

About 18% of children younger than 10 years and 16% to 31% of children 10 years and older with sickle cell disease (SCD) have evidence of PAH by screening echocardiography. In children with SCD, PAH is substantially more common in boys than in girls. It is also present in a greater proportion of children with SCD who experience more hemolysis, as indicated by a high reticulocyte count (i.e., typically greater than 4%) and frequent vasoocclusive pain crises.

The causes of PAH in children with SCD are believed to be multifactorial. Increased hemolysis causes an increase in intracellular free hemoglobin that scavenges NO, causing vasoconstriction and increasing expression of soluble endothelial-derived adhesion molecules. Hemolysis also increases erythrocyte arginase, increasing the degradation of arginine, a substrate for cellular NO production. Functional or anatomic asplenia may also cause platelet activation, endothelial red cell adhesion, and in situ pulmonary vasculature thrombosis, leading to PAH.

Pharmacotherapy Treatment Goals

Therapeutic goals for the treatment of PAH are aimed at reducing MPAP to slow the progression of irreversible pulmonary vascular changes, improve oxygenation, and improve functional capacity while avoiding clinical deterioration that leads to death or a need for atrial septostomy or lung transplantation.

Nitric Oxide

Inhaled NO is an exogenously administered gas used to promote pulmonary vasodilation and inhibit vascular muscle remodeling. Nitric oxide works by stimulating soluble guanylate cyclase in the vascular endothelium. Soluble guanylate cyclase promotes the conversion of guanosine monophosphate to cyclic guanylate monophosphate (cGMP). Increased intracellular cGMP increases calcium influx into the sarcoplasmic reticulum, which relaxes vascular smooth muscle; reduces cell proliferation by increasing the activity of cyclic adenosine monophosphate (cAMP)- and cGMP-dependent protein kinases; and causes vasodilation by inhibiting cAMP degradation.

Inhaled NO can also improve ventilation-perfusion mismatch caused by poor pulmonary function, because inhaled NO will only be taken into ventilated alveoli, where it preferentially vasodilates the local pulmonary vasculature, shunting right ventricular output away from poorly ventilated and atelectatic lung tissue. Nitric oxide rapidly binds to iron on heme proteins, limiting the systemic effects of the drug. Its 2-second to 5-second half-life makes inhaled NO rapidly titratable. Inhaled NO lacks systemic vasodilatory effects in concentrations up to 80 ppm. Methemoglobinemia usually remains less than 1% when inhaled NO is administered at a concentration of 20 ppm, the usual maximal effective dose; however, it may increase to 5% or more if the drug is given at a concentration of 80 ppm.

Nitric oxide is commonly used as a first-line drug for the immediate control of severe symptomatic PAH in patients in the pediatric ICU. Inhaled NO is preferred over hyperventilation and oxygen for severe PAH because it does not cause the reduction in cardiac output or the increase in systemic vascular resistance seen after treatment with hyperventilation and oxygen. Although inhaled NO reduces the duration of mechanical ventilation in children after cardiac surgery, it is not currently recommended for prophylaxis or chronic treatment of PAH. Nitric oxide has not been shown to improve survival or shorten the duration of ICU stay in children after cardiac surgery.

Nitric oxide may be acutely indicated in patients who, despite mechanical ventilation with an FiO_2 of 100%, have elevated MPAPs or right ventricular pressures and hemodynamic lability. Figure 1-1 gives an algorithm for the initiation, titration, and discontinuation of inhaled NO in children with PAH associated with CHD. Similar algorithms with different titration guidelines and expectations could be made for children with other types of cardiac anatomy.

Children with right-to-left shunt-dependent CHD should not receive inhaled NO because it could lead to clinical deterioration. Similarly, children with severe left ventricular dysfunction should not receive inhaled NO because it may cause pulmonary edema secondary to increased pulmonary capillary wedge pressure. Children with pulmonary venous obstruction should
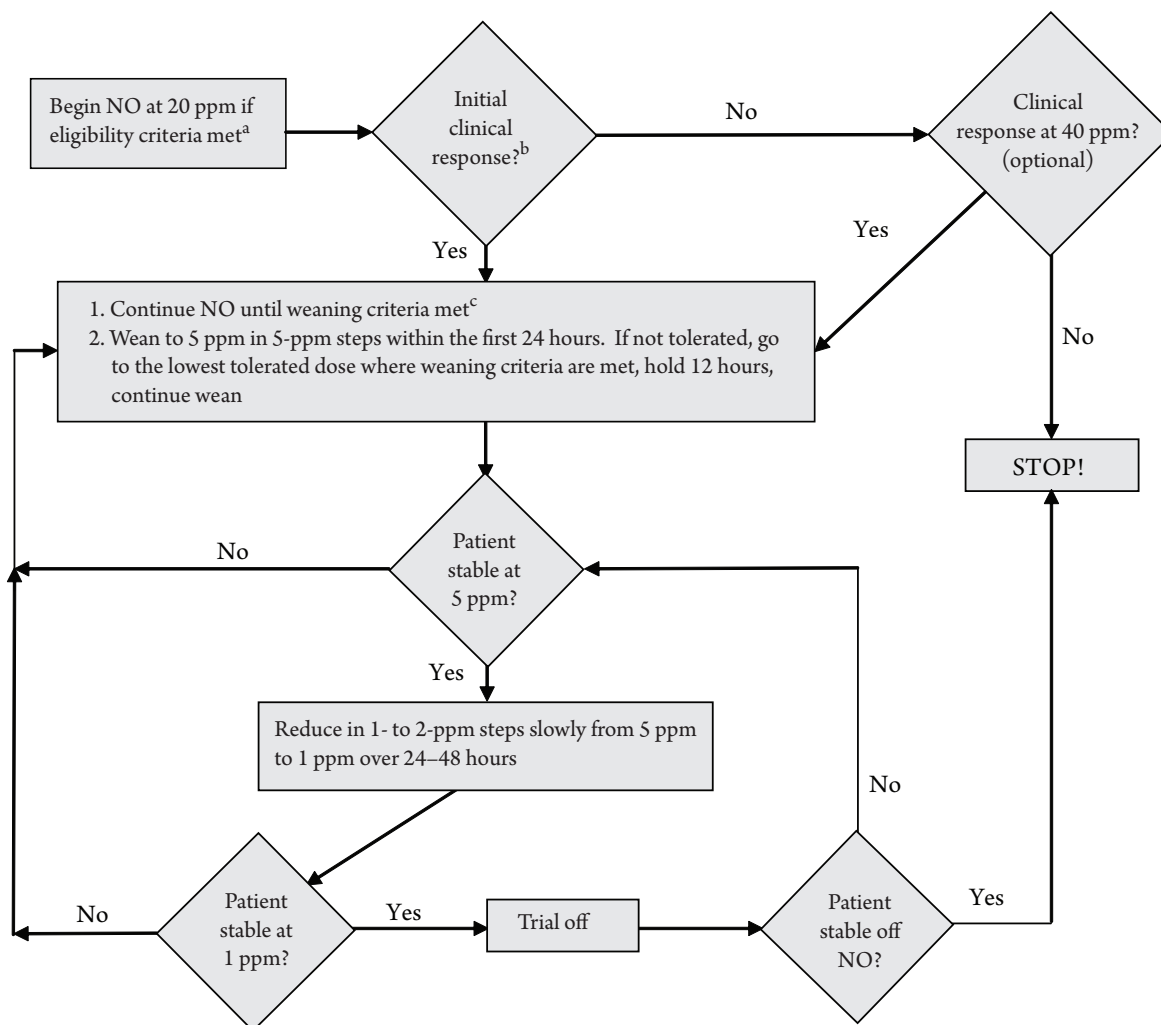
Figure 1-1. Treatment algorithm for inhaled nitric oxide for infants and children after cardiac surgery; status: biventricular (non-mixing).

[a]Eligibility criteria: S/P cardiac surgery, ventilator + 100% FiO_2, MPAP or RVP ≥ 65% SAP, and hemodynamic lability.

[b]Clinical response: occurs in < 60 minutes, response includes: ↑ ΔPaO_2 > 20 mm Hg or ↓ $\Delta MPAP$ ≥ 10 mm Hg.

[c]Weaning criteria: FiO_2 < 60%, PaO_2 > 60 mm Hg and MPAP ≤ 65% SAP or SaO_2 ≥ 80% (may use < 80% at the discretion of the clinician)

FiO_2 = fractional concentration of oxygen in inspired gas; MPAP = mean pulmonary arterial pressure; NO = nitric oxide; PaO_2 = partial pressure of oxygen; RVP = right ventricular pressure; SaO_2 = blood oxygen saturation; SAP = systemic arterial pressure; S/P = status post; ppm = parts per million.

Δ = change in; ↓ = decrease; ↑ = increase; R→L = right-to-left.

not receive inhaled NO because it will cause transient improvement and then deterioration.

Finally, inhaled NO commonly causes rebound PAH if it is discontinued abruptly, even in patients who do not derive any initial benefit from it. This rebound PAH is likely caused by down-regulation of endogenous NO synthase activity in the presence of exogenous NO. A slow wean (e.g., reduce total dose in 5-ppm increments to a total dose of 5 ppm and then reduce the dose in 1-ppm to 2-ppm increments over 24 hours) is usually effective in preventing rebound PAH. However, administering an additional drug effective for PAH may be warranted if the patient is experiencing difficulty even with a slow wean. Both a continuous epoprostenol infusion and a single dose of sildenafil help children wean from NO.

Nitric oxide can substantially reduce the signs and symptoms of PAH in select populations of children. However, it should not be used in patients unless its benefit is clearly possible because the drug is quite expensive,

costing health systems and governments millions of dollars per year. Because NO is an inhaled gas, its use is limited to institutions.

Calcium Channel Blockers

Although only about 5% to 10% of children with vasoresponsive PAH obtain symptom relief with calcium channel blockers, it is still reasonable to try one of these agents as first-line treatment for children with vasoresponsive PAH. Children receiving calcium channel blockers who do not have symptom improvement into WHO functional class I or II should be considered nonresponders, and alternative treatment of PAH should be initiated.

Long-term, uncontrolled trials of children whose PAH has responded to calcium channel blockers have found prolonged survival rates similar to those of adults. Nifedipine and amlodipine are most commonly used. Amlodipine is the better choice because it is not associated with significant rebound tachycardia. In addition, its long half-life allows once-daily administration as a tablet or an extemporaneously compounded suspension without the need for a sustained-release delivery mechanism. Nifedipine is less desirable because it is short-acting and lacks a sustained-release product that can be administered to children. Furthermore, nifedipine can cause rebound tachycardia because of its vasodilatory effects. Using verapamil for the treatment of children with PAH has not been described. Verapamil should not be used for treating infants with PAH because it can cause life-threatening hypotension and bradycardia, and its use has been associated with sudden cardiac death after intravenous administration.

The effectiveness of calcium channel blockers in patients with PAH declines with time, such that less than 50% of children who respond initially continue to respond 10 years after initiating therapy. Therefore, repeat cardiac catheterization should be conducted at least yearly to determine whether the drug's effect is decreasing. Calcium channel blockers should be avoided in children with PAH who do not respond to the vasoresponsiveness challenge because of the potential for hypotension and right ventricular failure.

PDE-5 Inhibitors
Sildenafil

Sildenafil promotes pulmonary vasodilation in children with PAH through the inhibition of pulmonary PDE-5; this causes increased cellular cGMP concentrations that result in increased intracellular calcium concentrations. Systemic vasodilation is limited at therapeutic sildenafil dosages because PDE-5 is primarily found in lung and penile tissues. Sildenafil also inhibits PDE-6 and PDE-1, which are up-regulated in PAH, and their inhibition may cause a cAMP-mediated antiproliferative effect. Research suggests that sildenafil also reduces plasma concentrations of endothelin-1, an important mediator in PAH.

Orally administered sildenafil is often used early in the course of PAH and in patients with less severe disease (e.g., WHO functional classes II and III) because it is more convenient than intravenous or inhaled therapies, and it produces fewer adverse effects in children than other oral therapies. Some studies with small sample sizes provide limited evidence to support sildenafil use in children with PAH. Overall, sildenafil has been shown to reduce MPAP and pulmonary vascular resistance and improve exercise tolerance as measured by the 6-minute walk test. Sildenafil is also helpful in weaning children in the ICU from inhaled NO. It may be less useful as monotherapy for long-term use because of tachyphylaxis, but this effect needs further study. The normal starting oral sildenafil dose for children with PAH is 0.25–0.5 mg/kg given every 4–8 hours. If this dose is ineffective, it should be increased, as tolerated, up to 1 mg/kg given every 4–8 hours. The use of sildenafil doses as high as 2 mg/kg has been reported. Sildenafil can be formulated into an oral suspension from bulk powder or by crushing sildenafil tablets.

Like oral sildenafil, intravenous sildenafil reduces pulmonary vascular resistance. Studies in postoperative infants and children with CHD found that it lowers pulmonary vascular resistance to a similar extent as inhaled NO. It can further lower pulmonary vascular resistance in patients receiving 20 ppm of inhaled NO. However, intravenous sildenafil can increase intrapulmonary shunting, reduce systemic blood pressure, and impair oxygenation in the postoperative pediatric cardiac population. Doses from 0.25–0.35 mg/kg intravenously have been studied in pediatric patients.

The most common adverse effects of sildenafil are headache, nasal congestion or bleeding, dyspepsia, and flushing caused by extrapulmonary PDE-5 inhibition as doses are escalated. Inhibition of retinal PDE-6 can cause blurred vision, light sensitivity, and altered color vision. Sildenafil can cause substantial hypotension in patients also using nitrates for heart disease. Sildenafil is metabolized primarily by hepatic cytochrome P450 (CYP) 3A4 and, to a lesser extent, by hepatic CYP 2C9. Caution should be exercised when using sildenafil with other drugs that cause either induction or inhibition of these enzyme systems. For example, plasma sildenafil concentrations are reduced by more than 50% when coadministered with bosentan, a CYP 3A4 and 2C9 inducer.

Tadalafil

Tadalafil is also a PDE-5 inhibitor and an alternative to sildenafil in children with PAH. It has a longer duration of action, allowing once-daily dosing. However, it is only available in tablet form, and adequate published data in children with PAH are lacking.

Endothelin Receptor Antagonists

Bosentan

Bosentan is a nonselective inhibitor of endothelin-1 at endothelin-A and endothelin-B receptors. Endothelin-1 is normally released from the vascular endothelium and is one of the most potent vasoconstrictors known. Endothelin-1 is found in elevated concentrations in the plasma and tissues of children with PAH. Action of endothelin-1 at the endothelin-A and endothelin-B receptors on pulmonary artery smooth muscle cells causes constriction and remodeling in patients with PAH. However, binding of endothelin-1 to the endothelin-B receptor found on the endothelial cell causes NO release, which may protect against pulmonary vasoconstriction. It is believed that the vasoconstricting qualities of endothelin-B are up-regulated and that its vasodilating actions are down-regulated in patients with PAH.

Like sildenafil, bosentan is usually used in children with PAH with less severe disease (e.g., WHO functional classes II and III). Bosentan has been shown to improve pulmonary hemodynamics, functional and exercise capacity, and survival in children with idiopathic PAH and PAH associated with CHD. However, some evidence shows that exercise capacity diminishes when the drug is taken for longer than 1 year.

Bosentan is more convenient than the parenteral drugs used for PAH because it is administered orally twice daily, but it is only available as a tablet and is only stable in suspension for 24 hours. Therefore, the tablet must be cut into measurable amounts (e.g., one-half or one-fourth tablet) or compounded into a suspension daily for smaller children who cannot swallow tablets. A dispersible formulation is available in Europe. Adverse effects of bosentan include hepatotoxicity, peripheral edema, and anemia. In addition, it is an inducer of hepatic CYP 3A4, 2C9, and possibly 2C19, and may affect the clearance of other drugs metabolized by these pathways. Bosentan does not affect epoprostenol clearance. Liver enzyme tests should be assessed monthly because elevations have been reported in up to 14% of patients receiving bosentan. Bosentan is teratogenic and should be avoided in women who are pregnant or who may become pregnant. Effective and reliable birth control should be used if bosentan is taken by a young woman who may become pregnant.

Ambrisentan

Ambrisentan is a selective endothelin-A receptor antagonist with fewer expected adverse effects, fewer drug interactions, and lower hepatotoxicity rates than bosentan. Although the drug is expected to improve exercise capacity and delay clinical deterioration in patients with PAH, similarly to bosentan, it has been inadequately studied in children and is therefore seldom used. Ambrisentan is also teratogenic. Ambrisentan is U.S. Food and Drug Administration (FDA)-labelled for use in the treatment of adults with PAH WHO functional class I and in those with WHO functional class II and III symptoms to improve exercise capacity and delay clinical deterioration.

Prostanoids

Epoprostenol

Epoprostenol is the sodium salt of prostacyclin (i.e., prostaglandin I_2). Epoprostenol and the other prostacyclin analogs cause vasodilation by increasing arteriolar cAMP. They also reduce platelet adhesion and pulmonary arteriolar remodeling. Epoprostenol is considered the gold standard for treatment of children with idiopathic PAH, severe PAH (i.e., WHO functional classes III and IV), or PAH that is not vasoresponsive. Epoprostenol improves pulmonary hemodynamics, quality of life, functional capacity, and survival in children with idiopathic PAH and PAH associated with CHD. The effects of epoprostenol are additive to those of NO; therefore, epoprostenol may be used concomitantly with NO in the ICU to control acutely elevated MPAPs or to assist in weaning a patient off inhaled NO.

Epoprostenol is usually initiated at 1–2 ng/kg/minute as a continuous infusion through a dedicated lumen of a central venous catheter. The dose is then increased in 1-ng/kg/minute to 2-ng/kg/minute increments every 15 minutes until additional beneficial effects are no longer observed or until adverse effects occur. Common adverse effects that indicate acute epoprostenol overdose include flushing, headache, diarrhea, hypotension, tachycardia, nausea, and vomiting. If substantial adverse effects occur, the dose should be reduced in 2-ng/kg/minute increments every 15 minutes. Clinically significant rebound PAH, which may be fatal, can occur with abrupt discontinuation or large dosage reductions of epoprostenol.

The half-life of epoprostenol is about 2–5 minutes; therefore, it must be given by continuous intravenous infusion without interruption. Epoprostenol expires after 8 hours at room temperature; thus, 24-hour infusions are usually kept cold with ice packs that are changed every 12 hours. A back-up epoprostenol infusion solution must always be prepared and kept under refrigeration while an infusion is running in case the solution unexpectedly runs out. Chronically, the optimal epoprostenol dosage is 50–80 ng/kg/minute in children and 20–40 ng/kg/minute in adults.

The most common chronic adverse effects from epoprostenol are jaw pain and diarrhea. Rash, muscle pain, and headache are also reported. Central venous catheter infections with bacterial organisms, primarily *Staphylococcus*, are an important complication of intravenous epoprostenol. Clinicians and caregivers must continuously observe the patient for signs of catheter sepsis (e.g., fever, confusion, lethargy). Inhaled epoprostenol has been used in lieu of NO in critically ill children, but published dosage and efficacy studies are lacking.

Treprostinil

Treprostinil is a prostacyclin analog that may be considered in children with WHO functional class II–IV PAH who have been stabilized on epoprostenol. Treprostinil has an elimination half-life of about 4 hours and is stable at room temperature after reconstitution. It may be given intravenously, subcutaneously, or inhaled. An equivalent dose of intravenous treprostinil is about 1.5–4 times the epoprostenol dose. Children who are converted from epoprostenol to treprostinil experience more than a 50% reduction in headache, rash, facial and palmar flushing, jaw pain, diarrhea, and other gastrointestinal complaints; this reduction can be sustained for 6–12 months after conversion.

As with epoprostenol, patients receiving treprostinil should be carefully observed for symptoms (e.g., confusion, lethargy) of central venous catheter infection with bacterial organisms, primarily *Staphylococcus*. Subcutaneous treprostinil is not used in children because of pain, induration, and the potential for ulceration at the injection site. In 2009, the FDA approved the labeling for treprostinil as a metered-dose inhaler given in a dosage of three puffs (18 mcg) four times/day for the treatment of PAH in patients with functional class III symptoms. However, the drug has not been studied in children or patients with preexisting bronchospastic lung disease.

Iloprost

Iloprost is a prostacyclin analog indicated for adults with WHO functional class III or IV pulmonary hypertension. Its half-life is about 20–30 minutes. Both intravenous and inhaled iloprost cause a significant reduction in MPAP. Nebulization of iloprost localizes its effect in the lungs while minimizing systemic hemodynamic adverse effects, although it can cause cutaneous vasodilation around the mouth and bronchoconstriction in about one-third of children.

Similar to inhaled NO, iloprost inhalation improves ventilation-perfusion mismatch when the cardiac output is perfusing poorly ventilated or atelectatic lung tissue. Inhaled iloprost causes a reduction in MPAP similar to inhaled NO in children with idiopathic PAH and PAH related to CHD. Iloprost can be a useful treatment in children with acute pulmonary hypertensive crisis after CHD repair when inhaled NO is unavailable.

In children 12 years and older, inhaled iloprost is usually initiated as a 2.5 mcg/dose administered every 2 hours, with six to nine doses given per day. The dose may be increased to 5 mcg, if tolerated. Caution should be used in pediatrics because the dose is not standardized for weight. Each nebulization takes about 15 minutes to deliver. It is difficult for young children to use the delivery device and adhere to a 2-hour dosing schedule if the drug is needed chronically. Because of frequent dosing, inhaled iloprost is more commonly used in the ICU for the acute management of PAH or as add-on therapy or in refractory PAH after the failure of oral drugs. A combination of inhaled iloprost and bosentan or sildenafil appears to be tolerated by most older children.

Intravenous iloprost is not selective for the pulmonary vascular bed. Administration can cause a substantial reduction in systemic arterial pressure and hypotension, which may not be well tolerated in some children. However, only the inhaled form of iloprost has FDA approval. Dosing of intravenous iloprost in children is lacking outside of case series. A 25-ng/kg dose infused over 10 minutes was effective in a small group of children with PAH secondary to CHD.

Two proprietary nebulization devices are marketed in the United States for the delivery of inhaled iloprost. Each generates iloprost in droplet sizes between 2.5 micrometers and 5 micrometers. Little information is available on the effectiveness and adsorption of nebulized iloprost to guide appropriate dosing in children.

Anticoagulation

Anticoagulation with warfarin should be considered in older children at a higher risk of pulmonary embolism, such as those with chronic progressive PAH, idiopathic PAH, PAH with reduced cardiac output, severe polycythemia, or other clotting risk factors. Anticoagulation is also indicated for patients with more advanced disease (e.g., WHO functional classes III and IV) or those on continuous intravenous treatment. Low-dose aspirin (3–10 mg/kg/day) is sometimes used in younger children, but its relative benefit compared with warfarin is unclear in this population. Given the evidence in adults, aspirin is a secondary option in children when warfarin is contraindicated.

The rationale for anticoagulation is based on improved survival in five of seven studies of adults. The most common populations studied were adults with idiopathic, heritable, and anorexigen-related PAH with WHO functional classes III and IV. Data regarding the clinical outcomes of anticoagulation in children with PAH are lacking. However, if used, the international normalized ratio (INR) should be titrated to 1.5–2.5.

Conclusion

Pulmonary arterial hypertension is an exciting area of research and pharmaceutical development because of its multifactorial etiology and poor prognosis. Many treatments unavailable 10–15 years ago are being used in children today. Further investigation likely will improve the care of children with PAH in the future.

Annotated Bibliography

1. Vlasselaers D, Milants I, Desmet L, Wouters PJ, Vanhorebeek I, van den Heuvel I, et al. Intensive insulin therapy for patients in paediatric intensive care:

a prospective, randomised controlled study. Lancet 2009;373:547–56.

This study was a prospective, randomized, controlled single-center evaluation of the glucose control protocol established by investigators in Leuven, Belgium, now known as the Leuven protocol. The investigators included 700 critically ill infants and children randomized to achieve either a conventional glucose target (blood glucose concentration: 216 mg/dL or lower) or an intensive glucose target with insulin (blood glucose concentrations: infants, 51–80 mg/dL; children, 71–102 mg/dL). The primary end points of the study were duration of ICU stay and inflammation. Secondary end points were duration of mechanical ventilation and other vital organ support, biochemical markers of organ dysfunction, secondary infections, mortality, symptoms related to hypoglycemia, time to normalization of blood glucose, and highest blood glucose concentration reached within 4 hours of a hypoglycemic event. Analysis was conducted by an intention-to-treat approach.

The investigators found the intensive target group had significant reductions in ICU length of stay (i.e., −0.64 fewer days), C-reactive protein concentration at day 5 (i.e., −0.87 mg/L), mortality (−3% absolute reduction; 50% relative reduction), and secondary pulmonary and bloodstream infections (−7.6% absolute reduction) compared with the conventional target group. Blood glucose concentrations of 40 mg/dL or less were reported in 25% of the intensive target group and 1% of the conventional group.

This study is important because it was a large, prospective, and controlled comparison of the effects of insulin, differing from the many retrospective and uncontrolled studies of HCI in children. The investigators found small but important improvements in several primary and secondary clinical outcomes. Unfortunately, patients in the tight glycemic target group experienced considerably more hypoglycemia than those in the conventional glycemic target group. In the intensive control group, 25% and 5% of the patients experienced blood glucose concentrations less than 40 mg/dL and less than 31 mg/dL, respectively.

2. Preissig CM, Hansen I, Roerig PL, Rigby MR. A protocolized approach to identify and manage hyperglycemia in a pediatric critical care unit. Pediatr Crit Care Med 2008;9:581–8.

In this article, the investigators described the Emory pediatric hyperglycemia protocol, a stepwise guideline using insulin to control the blood glucose concentrations of critically ill children within a more permissive intermediate hyperglycemic range (80–140 mg/dL). Two separate blood glucose concentrations greater than 140 mg/dL were required for protocol initiation. The investigators used point-of-care testing equipment that measured capillary blood glucose concentrations. Although the data were collected retrospectively and there was no control group, this study is useful because it is the first workable published protocol with clinical and statistical outcomes. The protocol appears to be safe, with an incidence of hypoglycemia that is not statistically different from a retrospectively reviewed group of patients who were not screened for HCI and were not on the protocol. As presented, this protocol could be adopted as is or modified for implementation at other institutions.

3. Preissig CM, Rigby MR, Maher KO. Glycemic control for postoperative pediatric cardiac patients. Pediatr Cardiol 2009;30:1098–104.

This retrospective chart review compared glucose concentrations and other outcomes achieved in 20 children after heart surgery who were treated with the Emory pediatric hyperglycemia protocol (see reference 2) with glucose concentrations in 100 similar patients who were not treated according to the protocol. Hyperglycemia occurred in 84% of the patients. A trigger of two blood glucose concentrations greater than 140 mg/dL was used to initiate the protocol. Insulin was given to maintain patients within an intermediate hyperglycemic range of 80–140 mg/dL. The investigators found that children with controlled blood glucose concentrations had significantly fewer days in the ICU (2.5 versus 7 days) and fewer days of mechanical ventilation (1.5 versus 4 days), as well as nonsignificant, lower rates of blood stream infection (0% versus 3%) and mortality (0% versus 5%) compared to the group with HCI. The study showed that the Emory protocol was effective at controlling blood glucose concentrations in this population. This study also showed a consistently low rate of hypoglycemia with use of the protocol. This study is helpful because it shows that the Emory protocol works well not only in a mixed population of critically ill children, as reported in the authors' previous work, but also in children after heart surgery.

4. Verhoeven JJ, Brand JB, van de Polder MM, Joosten KFM. Management of hyperglycemia in the pediatric intensive care unit; implementation of a glucose control protocol. Pediatr Crit Care Med 2009;10:648–52.

This single-center study evaluated the use of the Rotterdam glucose control protocol in 50 critically ill children with HCI. Patients experiencing two blood glucose concentrations greater than 145 mg/dL were treated after an insulin infusion algorithm to limit glycemic excursions (target glucose concentrations: 72–145 mg/dL). The investigators used graduated insulin infusion protocols for initiation based on the initial blood glucose concentration. Starting insulin dosages ranged from 0.02 unit/kg/hour to 0.05 unit/kg/hour. The protocol was successful in reducing the blood glucose concentration to less than 145 mg/dL within 12 hours in 94% of the patients. Blood glucose concentrations below the target range were reported in 30% of patients, and 6% of patients experienced a blood glucose concentration less than 47 mg/dL. This study is noteworthy because it is one of only a few published protocols describing blood glucose management in critically ill children. Unfortunately, it also produced a high rate of mild hypoglycemia.

5. Jeschke MG, Chinkes DL, Finnerty CC, Kulp G, Suman E, Norbury WB, et al. Pathophysiologic response to severe burn injury. Ann Surg 2008;248:387–401.

This study is the first of two publications to describe the acute and sustained clinical, hormonal, and metabolic outcomes in children with burns. The authors included 242 children who had suffered burns encompassing more than 30% of their body surface area. The article documents patient energy expenditure; muscle protein synthesis and breakdown; and changes in body composition, hormones, proteins, cytokines, hepatic size, cardiac values, and physical functioning. This article provides a detailed review of the profound acute changes experienced by children after burn injury. The article also highlights the sustained nature of these changes, evaluating outcomes for up to 60 days after the burn injury. The blood glucose and insulin responses are measured and reviewed, indicating an acute rise in blood glucose concentration accompanied by a similar acute spike in blood insulin concentration. This finding suggests the presence of insulin resistance early in response to burn injury.

6. Gauglitz GG, Herndon DN, Kulp GA, Meyer WJ 3rd, Jeschke MG. Abnormal insulin sensitivity persists up to three years in pediatric patients post-burn. J Clin Endocrinol Metab 2009;94:1656–64.

This article is the second of two publications that describe the sustained clinical, hormonal, and metabolic outcomes observed in children after burn injury. The authors describe a prospective study of 194 children with burns over more than 40% of their body surface area. For a 3-year period after burn injury, urinary catecholamine and cortisol concentrations, serum cytokine and hormone concentrations, indirect calorimetry, growth, glycemic metabolic testing, and insulin sensitivity were assessed. This article is valuable because it shows the sustained effect of burn injury on numerous physiologic parameters. In particular, it shows that children with burns experience an early and elevated fasting blood glucose concentration that is sustained for 6 months after the burn. Fasting insulin concentrations did not reach statistically significant elevations until 6–9 months after the burn but remained elevated for up to 3 years.

7. Pham TN, Warren AJ, Phan HH, Molitor F, Greenhalgh DG, Palmieri TL. Impact of tight glycemic control in severely burned children. J Trauma 2005;59:1148–54.

This retrospective, observational chart review evaluated outcomes of intensive insulin treatment in children with burns covering 30% or more of their body surface area. The investigators compared the outcomes in 33 children whose blood glucose concentrations were controlled with insulin to a target range of 90–120 mg/dL with the outcomes in 31 historical controls whose blood glucose concentrations were not controlled (i.e., concentrations greater than 200 mg/dL were acceptable). The investigators found a lower incidence of urinary tract infections and a lower mortality in the group with a lower target range. This study is important because it directly compares a euglycemia target with a significant hyperglycemia target, showing that severely hyperglycemic children with burns have poorer outcomes than those whose blood glucose concentrations are maintained within a more physiologic range.

8. Ulate KP, Falcao GCL, Bielefeld MR, Morales JM, Rotta AT. Strict glycemic targets need not be so strict: a more permissive glycemic range for critically ill children. Pediatrics 2008;122:e898–e904.

This retrospective study assessed 177 children who underwent surgery for CHD and who were subsequently stratified according to their median blood glucose concentrations. Four groups were identified on the basis of their target glucose concentrations: euglycemia (60–125 mg/dL), permissive hyperglycemia (90–140 mg/dL), moderate hyperglycemia 140–179 mg/dL), and severe hyperglycemia (180 mg/dL or more). As in many other studies, the investigators found that mortality increased with higher sustained blood glucose concentrations (euglycemia 6.02%, permissive hyperglycemia 4.69%, moderate hyperglycemia 38.8%, and severe hyperglycemia 58.3%). However, this study is more interesting because it showed that higher mortality rates began in children with blood glucose concentrations of 140 mg/dL or greater. The study also showed that the mortality rate was lower in the permissive hyperglycemia range than in the euglycemia range, although this finding was not statistically significant. This relationship may be evidence of a J-shaped mortality curve in children with critical illness, where mortality appears to be lower in a permissive hyperglycemia range compared with a lower, euglycemic range or higher, more significant hyperglycemia (e.g., 140 mg/dL or more). Furthermore, patients in the permissive hyperglycemia range had fewer hypoglycemic episodes (17.2%) than those maintained in the euglycemia range (31.8%). A larger study with greater statistical power will be needed to confirm this mortality finding. If confirmed, insulin protocols with permissive glucose targets may benefit children with HCI and reduce the potential for hypoglycemic excursions.

9. Klein GW, Hojsak JM, Schmeidler J, Rapaport R. Hyperglycemia and outcome in the pediatric intensive care unit. J Pediatr 2008;153:379–84.

This study was a retrospective case series of 221 critically ill children with hyperglycemia on the first day of ICU admission. Patients with blood glucose concentrations greater than 200 mg/dL were compared with patients having blood glucose concentrations of 200 mg/dL or less. Patients with the higher blood glucose concentrations had worse outcomes. However, the outcomes in the groups were not statistically different after controlling for disease severity. Among the main criticisms of this study was the selection of a blood glucose concentration cutoff of 200 mg/dL to define hyperglycemia. In children, selection of a blood glucose concentration this high may not have been discriminating enough to avoid a type II error. Another shortcoming of the study is that it did not evaluate glucose concentration variability or time with elevated blood glucose concentrations, both of which have correlated with worse outcomes in other studies of children with HCI.

10. Yung M, Wilkins B, Norton L, Slater A; for the Paediatric Study Group, Australian and New Zealand Intensive Care Society. Glucose control, organ failure, and mortality in pediatric intensive care. Pediatr Crit Care Med 2008;9:147–52.

In this prospective inception cohort study, 409 critically ill children who were mechanically ventilated for longer than 12 hours were assessed for sustained hyperglycemia and various clinical outcomes. The results showed a significant association of area under the glucose time curve of greater than 110 mg/dL with mortality and organ dysfunction scores, even after controlling for disease severity. Hyperglycemia in the first 48 hours after ICU admission did not correlate well with organ dysfunction. This study showed a significant difference in patient outcomes with sustained and elevated blood glucose concentrations above a lower breakpoint for blood glucose concentration (i.e., 110 mg/dL) than other studies have used. This study is important because of its large sample size and its simple identification of a pediatric ICU population at high risk of HCI. However, the study was not controlled.

11. Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2009;54:S43–S54.

This publication contains a summary of the clinical classification of pulmonary hypertension as determined by the 4th World Symposium on Pulmonary Hypertension held at Dana Point, California, in 2008. The article is the most current consensus on the comprehensive causes of pulmonary hypertension. The article provides detailed summaries of each definition of the classification system with supporting references from the primary literature. Other detailed and useful summaries from the symposium covering various facets of pulmonary hypertension are also found in this journal supplement. This classification is good for clinicians who serve both adults and children to have a reputable and comprehensive source to identify and classify both common and rarer causes of pulmonary hypertension.

12. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association. Circulation 2009;119:2250–94.

This comprehensive consensus statement provides assessment, classification, mechanisms, clinical study review, and recommendations for the treatment of PAH. Although most of the publication is based on information in adults, it contains a section addressing PAH in children. The consensus guidelines recommend treatment with high-dose calcium channel blockade in vasoresponsive children. An endothelin receptor antagonist, PDE-5 inhibitor, or prostanoid should be administered to nonresponders and responders who continue in WHO functional class III after initial treatment. Children with WHO functional class III or IV PAH who do not improve with an endothelin receptor antagonist, PDE-5 inhibitor, or inhaled iloprost should be treated with an intravenous prostanoid. Although the section on children with PAH is comparatively short, this publication is the most current, comprehensive, and authoritative source on the classification and treatment of PAH in children.

13. National Pulmonary Hypertension Centres of the UK and Ireland. Consensus statement on the management of pulmonary hypertension in clinical practice in the UK and Ireland. Heart 2008;94(suppl 1):i1–i41.

This comprehensive consensus statement for the UK and Ireland provides direct assessment, classification, clinical study review, and recommendations for the treatment of PAH, similar to the U.S. consensus paper. The publication primarily presents information in adults, but it also has a short section on PAH in children. The article presents a clear and concise stepwise algorithm for the treatment of PAH in children. The consensus statement recommends that children who respond to a pulmonary vasoactive challenge be initiated on a calcium channel blocker. Nonresponders with stable PAH and WHO functional classification II or III should begin with either bosentan or a prostanoid. Nonresponders with unstable PAH and WHO functional classification III or IV should be given epoprostenol. This article is authoritative – published by the National Pulmonary Hypertension Centres of the UK and Ireland – and is quite clear about the appropriate treatment of children with PAH. The included algorithm could easily be incorporated into clinical practice.

14. Black SM, Kumar S, Wiseman D, Ravi K, Wedgwood S, Ryzhov V, et al. Pediatric pulmonary hypertension: roles of endothelin-1 and nitric oxide. Clin Hemorheol Microcirc 2007;37:111–20.

This article provides a detailed review of the endothelin-1 and NO pathways involved in the pathophysiology of PAH. The relationship of endothelin-1 and oxidative stress injury through reactive oxygen species is described by reporting the pathologic mechanisms of numerous endogenous enzymes, chemicals, and free radical generators involved in the pathophysiology of PAH. The article is a good review for developing a better understanding of the mechanisms that promote PAH, and it provides future targets for drug therapy.

15. Raja SG, Danton MD, MacArthur KJ, Pollock JC. Effects of escalating doses of sildenafil on hemodynamics and gas exchange in children with pulmonary hypertension and congenital cardiac defects. J Cardiothorac Vasc Anesthes 2007;21:203–7.

This study is important because it shows the effects of escalating doses of enterally administered sildenafil on hemodynamics and arterial blood gas measurements in a subset of children receiving inhaled NO for PAH after heart surgery for CHD. The investigators found that a sildenafil dose of 0.5 mg/kg was as effective as a dose

of 2 mg/kg when given every 4 hours by a gastric tube. Although the study may be criticized for its small sample size (n=10), it produced the only clinical data available on which to base sildenafil dosing in critically ill children with PAH after heart surgery.

16. Ivy DD, Claussen L, Doran A. Transition of stable pediatric patients with pulmonary arterial hypertension from intravenous epoprostenol to intravenous treprostinil. Am J Cardiol 2007;99:696–8.

This study describes how to convert a child whose PAH is stable on epoprostenol to intravenous treprostinil. Both slow and rapid transition methods are discussed in detail. Each method appeared to provide a safe transition. The investigators initially titrated to a final treprostinil dosage of about 1.25–1.75 times the epoprostenol dosage and then monitored the children for up to 1 year, adjusting the dosage, as needed, to effect. Patients experienced considerably less headache, rash, diarrhea, jaw pain, and fewer gastrointestinal disturbances with treprostinil than with epoprostenol. Leg pain was the only prostanoid adverse effect for which the rate was unchanged after conversion to treprostinil. This publication is important because it provides the only published information regarding the conversion from epoprostenol to treprostinil in children. The manuscript provides useful information for the clinician wanting to minimize adverse effects from epoprostenol.

17. Ivy DD, Doran AK, Smith KJ, Mallory GB, Beghetti M, Barst RJ, et al. Short- and long-term effects of inhaled iloprost therapy in children with pulmonary arterial hypertension. J Am Coll Cardiol 2008;51:161–9.

This open-label study is the only published data set of reasonable size on the use of inhaled iloprost for chronic PAH in children. The researchers evaluated the effects of iloprost in 22 children with chronic idiopathic PAH and PAH associated with CHD. Iloprost was added to existing PAH therapy. After 6 months of therapy, 85% of patients had unchanged or improved WHO functional class. Six-minute walk tests improved in 38%, remained unchanged in 54%, and declined in 3% after 6 months of therapy.

Headache (36%), cough (23%), and dizziness (14%) were the most common adverse effects seen in the study subjects. These effects occurred most often during the first several days of therapy and improved with time. Six (27%) children dropped out of the study because of clinical deterioration. Two of these children died and four were converted to intravenous prostanoid therapy. This article is important because it shows how to dose inhaled iloprost in children with PAH. Dosages provided in this study will allow clinicians to give trials of inhaled prostanoid to children with PAH as an alternative to chronic intravenous epoprostenol therapy.