the duration of norepinephrine administration in the septic subgroup, over hydrocortisone administration alone. The mineralocorticoid activity of hydrocortisone alone, however, may be sufficient and should not exceed 200 mg/d (equivalent to about 100 mg/m$^2$/d) when given to adults (313–316). Hydrocortisone's mineralocorticoid activity is deemed to be equivalent to 150 μg/m$^2$/d of 9α-fludrocortisone when a total daily dose of 20–50 mg of hydrocortisone is reached.

Treatment with low-dose hydrocortisone for relative adrenal insufficiency has gained interest since the first randomized controlled trial (RCT) in adults with septic shock was published in 2002, proving a mortality benefit (276). A subsequent RCT in adults did not confirm a mortality advantage for the treatment with stress doses of hydrocortisone, leaving us with conflicting results (316). The pediatric literature lacks large RCTs evaluating the benefit of corticosteroids specifically in septic shock and refractory septic shock, and a pediatric meta-analysis evaluating the role of corticosteroids in shock did not demonstrate benefit (302). Trials in premature newborns, and other studies in children and adults have repeatedly shown a positive effect on the cardiovascular system by decreasing the duration and/or amount of catecholamines administered (2, 67, 284, 287, 317, 318).

Very high-dose corticosteroid administration in septic shock has previously been associated with higher infection rates. Several studies published since 2006 point to the possibility of infectious complications as a result of corticosteroid administration in adults and children. Steroid use was linked to disseminated candidiasis in a case report (319); however, infectious complications were not found to be increased by the administration of corticosteroids in children and adults with shock in other studies. Other side effects in patients receiving corticosteroids have been described, including hyperglycemia and bleeding. Concerns regarding the development of myopathy in association with corticosteroid therapy have been raised but not confirmed in either the adult or pediatric population with shock. A rise in sodium during corticosteroid administration was observed in several studies and self-resolves after discontinuation. Pediatric septic shock is associated with suppression of all aspects of adaptive immunity, and steroid use was associated with further depression of peripheral blood mononuclear cell adaptive immunity messenger RNA expression (320, 321).

Analysis of data obtained during the RESOLVE trial did not reveal treatment benefit associated with the administration of corticosteroids, but the concerns for higher mortality associated with corticosteroid administration raised by the analysis of the Pediatric Health Information System database were not corroborated (321). Studies in patients with serious infectious illnesses, that is, meningococcal meningitis, have shown cortisol production rates between 4 and 15 times the normal daily production rate of 5.7–12.5 mg/m$^2$ (277–279, 290, 322–325) of cortisol. Effects on the cardiovascular system in shock have been shown at the lower end of the stress dose range. Administration of stress doses as low as 0.18 mg/kg/hr of hydrocortisone (about 4 mg/kg/d) shorten the time to cessation of vasopressor support (median time 2 vs 7 d in the placebo group) without improving mortality in adults (326). In a single-center study of term neonates, the administration of 45 mg/m$^2$/d of hydrocortisone resulted in similar complication rates compared with historical controls and resulted in a statistically significant increase in blood pressure at 2, 6, 12, and 24 hours after initiation (67). Cortisol levels in adults after IV boluses of 50 mg of hydrocortisone given 6 hourly showed peak plasma cortisol levels over 100 μg/dL, and nadir levels remained elevated at 40–50 μg/dL (326). Among children, only those with fluid-refractory shock were found to have adrenal insufficiency (327).

### Persistent Pulmonary Artery Hypertension (PPHN) of the Newborn Therapy

Inhaled nitric oxide therapy is the treatment of choice for uncomplicated PPHN (328, 329). However, metabolic alkalinization remains an important initial resuscitative strategy during shock because PPHN can reverse when acidosis is corrected (330). For centers with access to inhaled nitric oxide, this is the only selective pulmonary vasodilator reported to be effective in reversal of PPHN (331–336). Milrinone may be added to improve heart function as tolerated (337, 338). Investigations support use of inhaled iloprost (synthetic analog of prostacyclin) or adenosine infusion as modes of therapy for PPHN (339–345). ECMO remains the therapy of choice for patients with refractory PPHN and sepsis (346–349).

### Extracorporeal Therapies

Various extracorporeal therapies such as ECMO, CRRT, and blood purification (hemofiltration, hemoperfusion, and therapeutic plasma exchange [TPE]) have been reported with various successes in the management of pediatric sepsis and septic shock. ECMO is a viable therapy for refractory septic shock in neonates and children (346–359). Neonates have comparably good outcomes (80% + survival) whether the indication for ECMO is refractory respiratory failure or refractory shock from sepsis. Pediatric and adult patients with sepsis have lower survival (historically ≤ 50%) than neonates, but experienced ECMO centers are now reporting survival rates approaching 75% (356–358) for refractory shock and 90% for refractory pneumonia (359). Although ECMO survival is similar in pediatric patients with and without sepsis, thrombotic complications are common in sepsis. Efforts are warranted to reduce ECMO-induced hemolysis because free heme scavenges nitric oxide, adenosine, and a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (a.k.a. von Willebrand factor-cleaving protease) leading to microvascular thrombosis, reversal of portal blood flow, and multiple organ failure (360–364). Severe hemolysis (plasma Hgb > 1 g/L) is associated with longer ECMO runs, more blood product administration, and increased mortality (362). Independent risk factors for hemolysis on ECMO include very negative inlet pressures, higher pump speeds, kinked or narrowed cannulae, and nonpediatric oxygenators (362). The risk of hemolysis can be mitigated by using the proper sized cannulas for age, avoiding excessive pump speeds, and maintaining the negative inlet pressure close to the specified pressure drop given by the manufacturer for the flow rate and never greater than –100 mm Hg (363, 364).