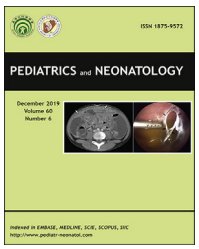
Pediatrics and Neonatology (2019) **60**, 603–610

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.pediatr-neonatol.com



Review Article

Late-onset glucocorticoid-responsive circulatory collapse in premature infants

Shigeo Iijima*

Department of Pediatrics, Hamamatsu University School of Medicine, 1-20-1 Handayama, Hamamatsu, Shizuoka 431-3192, Japan

Received Mar 21, 2019; received in revised form Jul 16, 2019; accepted Sep 6, 2019
Available online 12 September 2019

Key Words
adrenal insufficiency;
circulatory collapse;
glucocorticoid;
hypotension;
neonate

Late-onset glucocorticoid-responsive circulatory collapse (LGCC) in infants is characterized by sudden onset of hypotension and/or oliguria, which is resistant to volume expanders and inotropes but responds rapidly to intravenous glucocorticoids. LGCC occurs after the first week of life mainly in relatively stable very low birth weight (VLBW) infants. In Japan, the incidence of LGCC is reported to be 8%. Relative adrenal insufficiency (AI) is considered the most likely cause of LGCC, but its detailed pathophysiology remains unclear. Intrinsic and extrinsic factors may affect the pathophysiological mechanism. LGCC should be recognized as one of the high-risk complications in VLBW infants and managed promptly and properly, because if it is not, it may cause life-long neurological problems. To diagnose relative AI, an accurate evaluation of adrenal function is necessary; however, the interpretation of basal serum cortisol levels is difficult in preterm infants after 7 days of life. To recognize LGCC, it is recommended that blood pressure and urine volume be carefully monitored, even outside of the transitional period. If no underlying causes are documented or volume expansion and inotropic support fail, intravenous hydrocortisone should be initiated, and an additional dose of hydrocortisone is required when the response is inadequate. There are few reports to verify or characterize LGCC and this phenomenon has not been recognized worldwide to date. This review summarizes the current knowledge about LGCC in premature infants and evaluates the most significant new findings regarding its pathophysiology, treatment, and prognosis.

* Fax: +81 53 435 2312.
E-mail address: sige_pd@yahoo.co.jp.

https://doi.org/10.1016/j.pedneo.2019.09.005

1. Introduction

Very low birth weight (VLBW) infants are at risk of circulatory collapse during the immediate postnatal period. Signs and symptoms of circulatory collapse are similar to those of septic or cardiogenic shock. Since the 1990s, a subset of VLBW infants have experienced severe hypotension refractory to volume expanders and inotropes but responsive to glucocorticoids.[1–4] The underlying pathophysiology may be associated with impaired adrenal function in preterm infants.[5,6] Adrenal insufficiency (AI) usually occurs just after birth or within the first week of life and normalizes by the end of the second week.[2]

Since the early 2000s, cases of refractory hypotension after the first week of life have been reported.[7,8] In typical cases, VLBW infants are stabilized within the early neonatal period, and sudden subsequent onset of profound circulatory failure occurs. Most infants show sudden systemic hypotension and oliguria accompanied by hyponatremia and hyperkalemia and do not respond to conventional treatment with a volume expander or inotropic support. Glucocorticoid administration dramatically improves these conditions. The synchrony of this dramatic clinical course has prompted the recognition of a new condition, late-onset glucocorticoid-responsive circulatory collapse (LGCC), which differs from the recognized unstable circulatory status condition observed in premature infants soon after birth.[8] According to recent studies in Japan and Korea, a significant proportion of preterm infants may develop LGCC.[9–13] This condition may be due to relative AI associated with prematurity.[8,14]

No reports characterizing LGCC have been published in North America or Europe[15]; previous studies conducted in Japan and Korea have not provided comprehensive information. To assist pediatricians in recognizing this condition, our review summarizes current knowledge about the pathophysiology, treatment, and prognosis of LGCC in premature infants.

2. Definition and incidence

As the concept of LGCC has arisen from cumulative case reports, its clinical diagnostic criteria have not been established. However, the following tentative diagnostic criteria for late-onset circulatory collapse have been suggested by the Japanese Study Group for Neonatal Endocrinology: circulatory collapse occurs outside of the transitional period; a stable period exists before circulatory collapse onset; absence of apparent causes such as sepsis, symptomatic patent ductus arteriosus (PDA), massive bleeding, or necrotizing enterocolitis prior to circulatory collapse onset; presence of sudden-onset hypotension and/or oliguria; and the hypotension and/or oliguria is resistant to intravenous volume expanders and inotropes.[16,17] In the Neonatal Research Network, Japan (NRNJ) database, LGCC is defined as a clinical diagnosis based on the fulfilment of these diagnostic criteria and a response to glucocorticoids.[9]

According to the most recent nationwide NRNJ databases, LGCC incidence in VLBW infants was 8.0% in 54,893 VLBW infants between 2003 and 2016.[10] In Korea, an incidence of 5.4–6.7% was reported in infants born at <33 weeks' gestation.[12,13] According to Japanese studies comparing LGCC with non-LGCC, gestational age and birth weight were significantly lower in LGCC, but multivariate analyses revealed low gestational age to be significantly associated with an increased LGCC risk.[9,18] Regarding fetal growth, small for gestational age was shown to increase LGCC risk.[9]

3. Pathophysiology and potential associated factors

Glucocorticoid-responsive circulatory collapse in preterm infants usually develops within the first week of life because it represents a maladaptation to the early transition to extrauterine life.[2,4] Most affected infants have perinatal stress events leading to cortisol consumption.[15] However, in a Japanese study comparing severe neonatal conditions (e.g., low Apgar score, respiratory distress syndrome, pulmonary hemorrhage, and grade III/IV intraventricular hemorrhage) in LGCC and non-LGCC patients, there were no significant differences.[17] It is unclear why LGCC develops after 7 days of life in relatively stable VLBW infants. Intrinsic and extrinsic factors may affect the pathophysiological mechanism (Fig. 1). Underlying molecular mechanisms require further exploration.

3.1. Immature hypothalamic-pituitary-adrenal axis

Hormone activity in the hypothalamic-pituitary-adrenal (HPA) axis can be detected between 8 and 12 weeks' gestation and is established by 20 weeks' gestation.[19] However, the fetal adrenal cortex does not express 3-β-hydroxysteroid dehydrogenase (3β-HSD) before 23 weeks' gestation, and fetal adrenal glands use placental progesterone to bypass 3β-HSD and produce cortisol before 30 weeks' gestation.[3,19]

After birth, the major physiological roles of the adrenal cortex are to provide glucocorticoids for maintaining metabolic homeostasis and responding to stress, and to provide mineralocorticoids for maintaining fluid and electrolyte balance. As the adrenal axis is not fully functional by 30 weeks' gestation, premature infants born before 30 weeks have two factors contributing to adrenal dysfunction—developmental immaturity of adrenal enzyme expression and relative AI related to the HPA axis.[19,20] This hyporesponsive status of the adrenals is only transient; in most cases, the adrenal glands recover their function substantially by 14 days of life.[2,21] However, in some very premature infants, inadequate adrenocortical response may be prolonged beyond the second week of life.[1,6] A study found that serum cortisol levels did not differ in LGCC and non-LGCC infants but that LGCC infants had significantly elevated cortisol precursors, suggesting limited 3β-HSD.[14] Moreover, limited response to corticotrophin-releasing hormone (CRH) tests at 2 weeks of life in infants born before 30 weeks' gestation was reported,[22] suggesting that relative AI is likely even after the transitional period in very preterm infants.

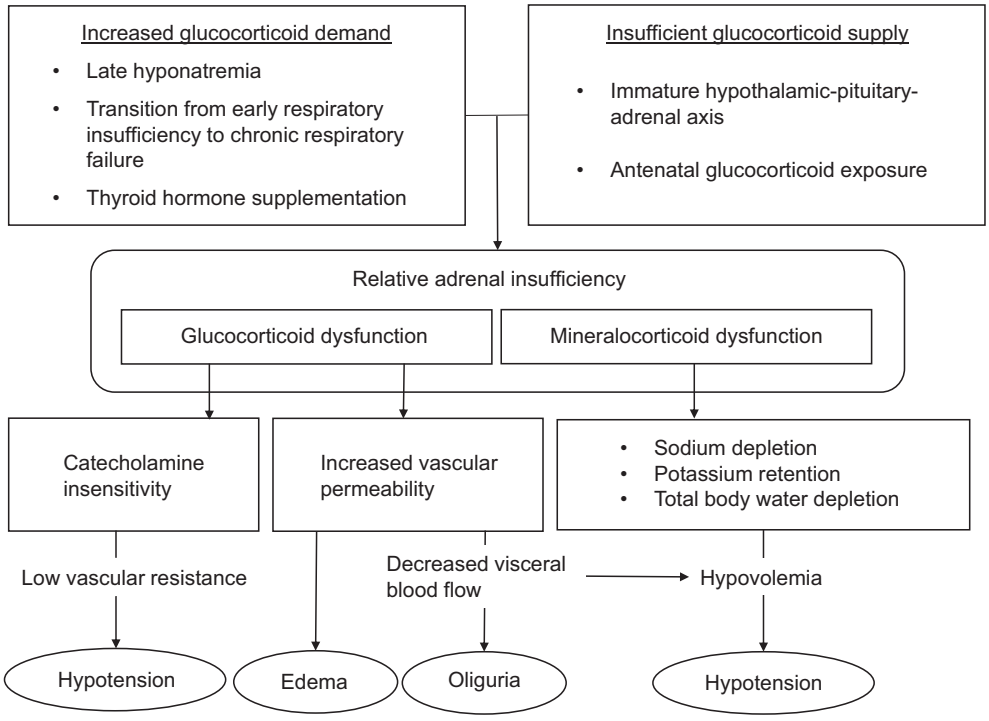


Figure 1 Mechanism of late-onset glucocorticoid-responsive circulatory dysfunction in preterm infants.

3.2. Antenatal glucocorticoids

Synthetic glucocorticoids, such as betamethasone, are widely administered to pregnant women at risk of premature delivery to improve lung development and survival in premature infants born before 34 weeks' gestation.[23] Antenatal glucocorticoid use, which suppresses neonatal adrenal function in the early period after birth, is a cause of transient AI of prematurity.[2,15] Some studies in Japan demonstrated that antenatal glucocorticoid use was significantly higher in LGCC infants than in non-LGCC infants.[9,18] Previous studies have shown suppression of the HPA axis at baseline and in response to a physiologic stressor during the first postnatal week following antenatal corticosteroid therapy.[23] Although these studies demonstrated a return to normal baseline cortisol levels within a week after antenatal glucocorticoid treatment, some long-lasting programming effects of this treatment on the HPA axis and stress responses have been observed in humans.[23] Infants exposed to antenatal glucocorticoids may have lower responses to CRH tests approximately 2 weeks after birth.[22] Therefore, antenatal steroids may increase the risk of relative AI beyond the transitional period. However, no alternative to antenatal glucocorticoids exists for accelerating fetal lung maturation.

3.3. Transition from early respiratory insufficiency to chronic respiratory failure

VLBW infants often have gradual deterioration of gas exchange and require respiratory support and increased inspired oxygen concentrations during the weeks following birth, even though acute respiratory disease initially improves.[24] In a Japanese study, at the time of LGCC diagnosis, a higher percentage of infants required respiratory support and experienced respiratory status deterioration before the onset of LGCC compared to gestational age-matched non-LGCC patients.[17] Cortisol might be a key factor in respiratory course after the acute period, although multiple pathogenic factors may be involved. A study revealed insufficient adrenal responses to stress in sick and ventilated infants born at $<$30 weeks' gestation compared with nonventilated less sick preterm infants.[5] Moreover, weak HPA axis responses to CRH tests at 7 days of life were shown in VLBW infants requiring mechanical ventilation,[21] suggesting that these neonates are unable to secrete adequate amounts of cortisol under increased stress, leaving them vulnerable to continuing lung injury.

3.4. Late hyponatremia

Late hyponatremia, frequently occurring between 2 and 6 weeks of life in VLBW infants, is explained by excessive loss of renal sodium due to unresponsiveness of the distal renal tubule to aldosterone.[25,26] In this condition, glucocorticoids have a mineralocorticoid-like action in defending infants against hyponatremia.[27] If glucocorticoid does not increase because of an inadequate adrenal response when hyponatremia is refractory to aldosterone, circulatory collapse due to AI may develop. A study found that infants with LGCC had significantly lower serum sodium levels than those without LGCC at 7–14 days of life.[18]

3.5. Thyroid hormone supplementation

Transient hypothyroxinemia of prematurity is a common problem in VLBW infants after 7 days of life.[11] However, effectiveness of thyroid hormone supplementation in these

infants remains controversial because several cases of circulatory collapse associated with levothyroxine administration to VLBW infants have been reported.[11] AI becomes apparent if patients with panhypopituitarism receive thyroid hormone replacement without glucocorticoids.[28] This is because thyroid hormones increase cortisol metabolism and clearance, as well as glucocorticoid requirement. As premature infants are at high risk for AI, levothyroxine may induce relative AI.

4. Clinical characteristics

4.1. LGCC onset

A Japanese study reported a median age at the time of LGCC diagnosis of 16 days of life and 29 weeks of postmenstrual age.[17] In a Korean study, LGCC developed a median of 16.5 days after birth and the onset peaked at 11—15 days after birth.[12] All infants in these studies were in a relatively stable condition without prodromal signs at the time of LGCC onset.

4.2. Generalized edema and weight gain

Besides hypotension and oliguria, peripheral edema is one of the most remarkable symptoms of LGCC. At LGCC onset, body weight significantly increases, probably because of edema.[29] Blood volume does not increase, and cardiac failure is not seen in LGCC. The use of intravenous normal saline in infants with LGCC usually aggravates edema without improving intravascular blood volume or uresis,[7] suggesting that increased vascular permeability or increased capillary leakage contribute to the underlying pathophysiology of edema in LGCC. In sick preterm neonates, protein leakage occurs in numerous clinical situations due to prematurity. In this case, latently decreased colloid osmotic pressure due to persistent hypoalbuminemia may have caused the development of capillary leak and contributed to edema formation. However, to our knowledge, hypoalbuminemia has not been reported in LGCC patients. Therefore, it may be possible to distinguish relative AI from simple protein leakage based on the presence of a normal serum albumin level. However, normal serum albumin levels have proved difficult to define in neonates because serum albumin levels increase with gestation.[30]

4.3. Electrolyte imbalance

One study reported a 52% rate of hyponatremia (serum sodium $<$130 mEq/L) and 34% rate of hyperkalemia (serum potassium $>$6.0 mEq/L) in LGCC patients.[12] In a study comparing LGCC infants with gestational age-matched non-LGCC controls, hyponatremia (serum sodium $<$130 mEq/L) and hyperkalemia (serum potassium $>$5.5 mEq/L) incidences were significantly higher in LGCC infants.[17] In many patients with LGCC, hyponatremia is resistant to sodium supplementation.[17,18] The amount of supplemented sodium excreted into urine suggests that renal tubular dysfunction is an underlying pathophysiology of LGCC.[16] In AI, inactivated Na^+/K^+-ATPase in the distal tubule results in renal sodium wasting and potassium retention and can lead to hyponatremia and hyperkalemia.

4.4. Ultrasonographic findings

Ultrasonographic examination of myocardial functions and organ blood flow is useful for assessing hemodynamic conditions in LGCC. Significantly increased ejection fractions and decreased end-systolic wall stress were shown in patients with LGCC,[31] suggesting decreased afterload in a hyperdynamic state. Moreover, diastolic blood flow velocity was significantly decreased in the renal and anterior cerebral arteries, whereas systolic velocity was maintained. Additionally, mean blood flow velocity increased in the superior mesenteric artery and decreased in the anterior cerebral arteries.[31] Therefore, the hemodynamic condition in LGCC is neither cardiogenic nor hypovolemic shock, but circulatory insufficiency with blood flow maldistribution, resembling distributive shock in sepsis.[32]

4.5. X-ray findings

Chest X-ray often reveals a hazy opacity, likely due to pulmonary edema with clinical manifestations such as generalized edema and weight gain. In a single-center Japanese study, 74% of LGCC patients showed a hazy pattern of increasing lung density.[33]

5. Challenges in relative adrenal insufficiency diagnosis

There are no definitive diagnostic criteria for relative AI in preterm infants. To diagnose relative AI, accurate evaluation of adrenal function is necessary, i.e., measuring serum cortisol levels during periods of stress.[14,25] Neither CRH nor ACTH stimulation tests—although they may provide the most reliable information on the HPA axis[2,21]—are practical in an acute clinical setting. Therefore, estimating unstimulated circulating serum cortisol is probably the most practicable laboratory test in an emergency situation of circulatory collapse. A serum cortisol level of $<$415 nmol/L is frequently used for diagnosing AI, but this level is based on relative AI in critically ill adults and critically ill term neonates.[34] An inappropriately low serum cortisol $<$200 nmol/L level is an essential feature highly suggestive of relative AI, and serum cortisol $>$350 nmol/L may indicate alternative diagnoses during the first 7 days of life.[2,15] However, the question remains as to what is an appropriate stress control level in a preterm infant. The reference range for cortisol values in healthy preterm infants within 2 weeks of life is reported to be 165 $\pm$ 25 nmol/L.[20] Preterm infants who are not actually ill may have low basal cortisol levels without apparent compromise,[35] making it less clear what a "normal" cortisol level should be. Regarding evaluation of basal cortisol levels after 7 days of life, preterm infants at 24—27 weeks' gestation show significant decreases in cortisol values with advancing postnatal age.[36] Moreover, basal cortisol levels do not differ in

preterm infants with or without late-onset relative AI.[14,37] As there is no consensus on the appropriate serum cortisol cut-off value that can reliably indicate relative AI in preterm infants outside of the transitional period, caution should be exercised when using a single measurement of cortisol to reflect the dynamic status of the HPA axis.[38] While it is useful to determine cortisol levels, blood sampling in preterm infants is limited by small blood volume, and the decision to start hydrocortisone should not depend on a result which may take hours or days to generate. Therefore, endocrinological assessments are not performed in most cases.

6. Challenges in prediction and prevention of LGCC

As LGCC occurs in the absence of obvious causes in infants who have overcome major respiratory and circulatory problems during the early neonatal period, LGCC onset is very difficult to predict. In most patients, indications of LGCC onset are not noticed, despite careful physical examination.[17] At this stage, it is recommended that only blood pressure and urine volume be carefully monitored, even outside the transitional period.

One previous study investigated the correlation between adrenal size and LGCC in VLBW infants using ultrasonography and concluded that infants with immature adrenal glands with no involutional change within 3 weeks after birth are vulnerable to LGCC.[39] The results suggested that ultrasonography can be useful in predicting subsequent occurrence of LGCC, without hormonal assessment.

Regarding the prevention of LGCC, prophylactic use of hydrocortisone for LGCC has not been studied to date. Based on randomized clinical trials enrolling extremely low birth weight infants, prophylaxis of early AI using low-dose hydrocortisone reduced the incidence of hypotension without adverse effects on neurodevelopment.[40] In these studies, prophylactic hydrocortisone was initiated at $<$48 h after birth and continued for 5—15 days.[40] However, in many cases, LGCC develops later than 2 weeks after birth.[17] If hydrocortisone prophylaxis for LGCC is planned, a long duration of administration might be required, and short- and long-term outcomes of this treatment have not been determined.

7. Treatment

To prevent tissue hypoperfusion and the resultant end organ damage, initial treatment for LGCC should be for prompt stabilization of circulation. A flow-chart for managing late-onset circulatory collapse is summarized in Fig. 2. If VLBW infants suddenly exhibit hypotension and/or oliguria after 7 days of life, treatable causes, such as hypovolemia due to sudden blood loss, poor cardiac contractility secondary to symptomatic PDA, infection, or high positive pressure ventilation impeding venous return to the heart, must be excluded. Hypovolemic infants should initially be treated with volume expanders (e.g., normal saline or 5% albumin 10—20 mL/kg/dose).[41] Infants with poor cardiac contractility should initially be treated with conventional doses (2—20 μg/kg/min) of dopamine and dobutamine to maintain acceptable blood pressure.

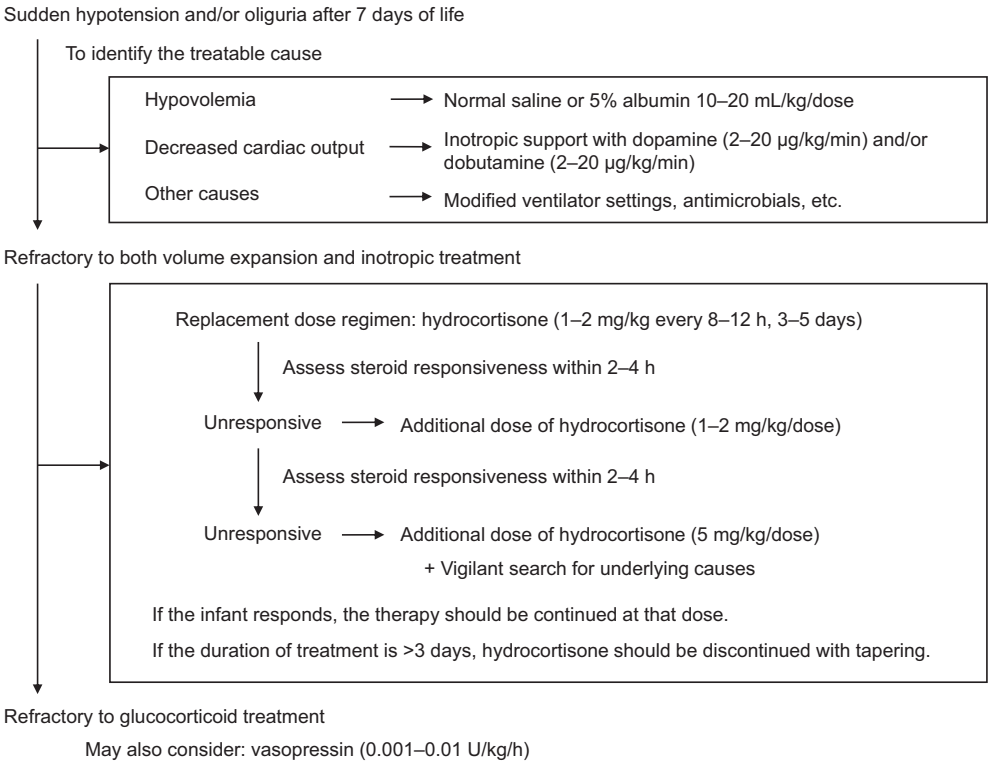


Figure 2 An approach to the management of late-onset circulatory collapse in very low birth weight infants.

In VLBW infants, hemodynamic effects and the clinical response to vasopressors and inotropes are altered by adrenergic receptor downregulation caused by critical illness-associated receptor stimulation.[42] In contrast, as cardiovascular adrenergic receptor expression is regulated by corticosteroids, relative AI contributes to the attenuated hemodynamic response and the development of vasopressor resistance in preterm neonates.[42] When underlying causes are not documented or volume expansion and conventional inotropic support fail, several therapeutic approaches have been attempted including additional escalation of dopamine treatment (>20 μg/kg/min),[42] addition of epinephrine,[43] and initiation of steroid administration.[4] However, high dopamine dose or epinephrine addition could theoretically carry the risk of severe α receptor-mediated vasoconstriction, resulting in decreased cardiac output and organ blood flow.[42] In that case, steroid administration offers a powerful tool to reverse adrenergic receptor downregulation because expression of cardiovascular adrenergic receptors is inducible by glucocorticoids. This transcriptional effect indirectly induces protein expression via transactivation through intracellular corticosteroid receptors (genomic effect). However, this effect is likely delayed because transactivation is a slow process that may take hours or even days.[44] In addition to this transcriptional effect, steroids exert certain non-genomic effects mediated by membrane-bound receptors, without transactivation, which affect the cardiovascular system without delay.[44] Therefore, in cases with volume- and pressor-resistant circulatory insufficiency in preterm infants, intravenous hydrocortisone should be administered. Although various dosage regimens have been used previously (Table 1),[1,3,4,15,16,45–50] common recommendations are 1–2 mg/kg (physiologic replacement dose: approximately 10–15 mg/m^2) every 8–12 h for 3–5 days.

Preterm infants with volume- and pressor-resistant shock may respond to hydrocortisone with a rapid increase in blood pressure within 1–2 h (non-genomic effects).[4,47] A study revealed that the median time from initial hydrocortisone administration to clinical condition improvement was 4 h (interquartile range: 3–5 h).[7] Therefore, when the response of an LGCC infant is inadequate within 2–4 h after the initial hydrocortisone dose is administered, re-dosing should be considered. Thus, after initial therapy, steroid responsiveness must be assessed. The parameters include improvement in blood pressure, improvement in urine output, and, ideally, improvement in splanchnic blood flow on ultrasonography. If such clinical responses are not confirmed, additional hydrocortisone administration (1–2 mg/kg/dose) is recommended. If there is still no response 2–4 h after the second hydrocortisone dose, an increased hydrocortisone dose (5 mg/kg/dose: approximately 50 mg/m^2/dose) should be administered. This dose is based on a recommendation for when adrenal crisis is suspected in a neonate with congenital adrenal hyperplasia.[51] If the infant responds, therapy continues at that dose. Timing of subsequent doses and weaning should be guided by the infant's clinical condition.

Alternatively, dexamethasone at a dose providing equivalent glucocorticoid potency as low-dose hydrocortisone can be used. However, since mineralocorticoids play an important role in the non-genomic effects of hydrocortisone, hydrocortisone is greatly preferred over dexamethasone for LGCC treatment.[52] A switch from hydrocortisone to dexamethasone therapy should be avoided because dexamethasone is associated with serious short- and long-term adverse effects, including growth restriction and neurodevelopmental impairments.[53]

When a stress dose of hydrocortisone is ineffective, intravenous vasopressin infusion (0.001–0.01 units/kg/h) may be considered.[54,55] Vasopressin is an anti-diuretic hormone analog that acts as a pure peripheral vasoconstrictor via vascular V1 receptor stimulation.[54] It safely increases blood pressure and is associated with increased urine output in VLBW infants with refractory hypotension.[55] Reported side effects of vasopressin with analog use include tissue hypoperfusion (mainly splanchnic) and digital and skin ischemia.[54] Vasopressin may prove promising for treatment of

Table 1 Dosing of hydrocortisone therapy for neonatal refractory hypotension.

Study	Initial therapy	Subsequent therapy
Hellbock et al., 1993[1]	24–60 mg/m^2/dose	–
Bourchier et al., 1997[45]	2.5 mg/kg/dose	Reducing dose over a 6-day period
Seri et al., 2001[4]	1 mg/kg every 12 h for 1–3 days 3–6 mg/kg/day twice or four times daily for 2–3 days	–
Efird et al., 2005[46]	1 mg/kg every 12 h for 2 days	0.3 mg/kg every 12 h for 3 days
Noori et al., 2006[47]	2 mg/kg/dose	1 mg/kg every 12 h
Fernandez et al., 2009[3]	1 mg/kg/dose	0.5 mg/kg every 12 h (if blood pressure improves within 2–6 h)
Johnson et al., 2015[48]	15 mg/m^2 or 1–2 mg/kg every 6–12 h	0.5 mg/kg/dose (if blood pressure and urine output improve within 24 h)
Watterberg, 2016[49]	1 mg/kg/dose	0.5 mg/kg every 12 h (if blood pressure improves within 2–4 h)
Ng, 2016[15]	1–2 mg/kg/dose	1 mg/kg every 8 h for 5 days 0.5 mg/kg every 12 h for 3 days
Peeples, 2017[50]	1 mg/kg/dose	0.5–1 mg/kg every 8–12 h
Kawai, 2017[16]	1–2 mg/kg/dose	–

hypotension in neonates with additional data; however, it is not currently recognized as a standard of care. Additional research is needed to determine appropriate timing and length of treatment, efficacy, and side effects.

8. Prognosis

8.1. Periventricular leukomalacia

As LGCC occurs at the most vulnerable time for white matter injury and some studies have demonstrated that central nervous system blood flow is decreased in LGCC patients,[31,56] LGCC may lead to periventricular leukomalacia (PVL), the most important cause of cerebral palsy in premature infants. A case—control study demonstrated that LGCC was a significant risk factor in the development of PVL.[57] Moreover, brain ultrasonographic findings of LGCC infants showed increased periventricular echogenicity after LGCC and PVL with rapid progression to macrocystic encephalomalacia.[13] Regarding long-term prognosis of LGCC, a Japanese study reported that LGCC infants were more likely to have cerebral palsy at 3 years of age than control infants.[29]

8.2. Retinopathy of prematurity

Retinopathy of prematurity (ROP) is still a leading cause of visual loss in childhood. As LGCC may mostly occur before ROP, circulatory and pulmonary failures due to LGCC can increase oxygen supply and thus worsen ROP. In a previous single-center study, comparisons between an LGCC and non-LGCC group indicated that the main problem related to LGCC might be frequent onset of subsequent ROP, and most LGCC cases developed severe ROP.[39] Moreover, LGCC was shown to be a useful predictive factor for treatment-requiring ROP and independently related to ROP severity.[58] Regarding the relationship between ROP and relative AI, a relationship between ROP and low cortisol response at 7 days of life is reported.[59] In addition, another study revealed that, in the presence of dopamine-resistant hypotension, low serum cortisol levels were significantly associated with severe ROP.[60] However, the influence of corticosteroid treatment for ROP in preterm infants is controversial as it has been variously reported as protective, harmful, and ineffective.[59]

9. Conclusions

Although LGCC may be due to relative AI associated with prematurity, it is very unique in terms of its onset after the transitional period and occurrence in relatively stable infants. LGCC should be diagnosed and treated rapidly because it may be a risk factor for PVL, cerebral palsy, and ROP. LGCC is well-known in Japan, but not widely recognized. Further research is required to improve the understanding of its pathophysiology and management.

Conflicts of interest

The author has no conflicts of interest to disclose.

References

1. Helbock HJ, Insoft RM, Conte FA. Glucocorticoid-responsive hypotension in extremely low birth weight newborns. *Pediatrics* 1993;**92**:715—7.
2. Ng PC, Lee CH, Lam CW, Ma KC, Fok TF, Chan IH, et al. Transient adrenocortical insufficiency of prematurity and systemic hypotension in very low birthweight infants. *Arch Dis Child Fetal Neonatal Ed* 2004;**89**:F119—26.
3. Fernandez EF, Watterberg KL. Relative adrenal insufficiency in the preterm and term infant. *J Perinatol* 2009;**29**:S44—9.
4. Seri I, Tan R, Evans J. Cardiovascular effects of hydrocortisone in preterm infants with pressor-resistant hypotension. *Pediatrics* 2001;**107**:1070—4.
5. Huysman MW, Hokken-Koelega AC, De Ridder MA, Sauer PJ. Adrenal function in sick very preterm infants. *Pediatr Res* 2000;**48**:629—33.
6. Watterberg KL, Gerdes JS, Cook KL. Impaired glucocorticoid synthesis in premature infants developing chronic lung disease. *Pediatr Res* 2001;**50**:190—5.
7. Shimokaze T, Akaba K, Saito E. Late-onset glucocorticoid-responsive circulatory collapse in preterm infants: clinical characteristics of 14 patients. *Tohoku J Exp Med* 2015;**235**:241—8.
8. Miwa M, Kusuda S, Ikeda K. International perspectives: late onset circulatory collapse in very low birth-weight infants: a Japanese perspective. *NeoReviews* 2009;**10**:e381—6.
9. Suzuki Y, Kono Y, Hayakawa T, Shimozawa H, Matano M, Yada Y, et al. Neonatal factors related to center variation in the incidence of late-onset circulatory collapse in extremely preterm infants. *PLoS One* 2018;**13**:e0198518.
10. NPO Neonatal Research Network, Japan. *Neonatal research network database Japan*. 2018. Available at http://plaza.umin.ac.jp/nrndata/. Accessed January 30, 2019.
11. Kawai M, Kusuda S, Cho K, Horikawa R, Takizawa F, Ono M, et al. Nationwide surveillance of circulatory collapse associated with levothyroxine administration in very-low-birthweight infants in Japan. *Pediatr Int* 2012;**54**:177—81.
12. Lee WJ, Kim MY, Cho HJ, Lee JS, Son DW. Clinical features of late-onset circulatory collapse in preterm infants. *Korean J Perinatol* 2013;**24**:148—57.
13. Shin SM, Chai JW. Brain ultrasonographic findings of late-onset circulatory dysfunction due to adrenal insufficiency in preterm infants. *Ultrasonography* 2016;**35**:258—64.
14. Masumoto K, Kusuda S, Aoyagi H, Tamura Y, Obonai T, Yamasaki C, et al. Comparison of serum cortisol concentrations in preterm infants with or without late-onset circulatory collapse due to adrenal insufficiency of prematurity. *Pediatr Res* 2008;**63**:686—90.
15. Ng PC. Adrenocortical insufficiency and refractory hypotension in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2016;**101**:F571—6.
16. Kawai M. Late-onset circulatory collapse of prematurity. *Pediatr Int* 2017;**59**:391—6.
17. Koyama N, Kouwaki M, Tanaka T, Ohki S, Iwase K, Terasawa S. Clinical features of late-onset circulatory dysfunction in premature infants. *Res Rep Neonatol* 2014;**4**:139—45.
18. Shimokaze T, Saito E, Akaba K. Increased incidence of late-onset circulatory collapse after changing clinical practice: a retrospective investigation of causative factors. *Am J Perinatol* 2015;**32**:1169—76.
19. Mesiano S, Jaffe RB. Developmental and functional biology of the primate fetal adrenal cortex. *Endocr Rev* 1997;**18**:378—403.
20. Quintos JB, Boney CM. Transient adrenal insufficiency in the premature newborn. *Curr Opin Endocrinol Diabetes Obes* 2010;**17**:8—12.
21. Ng PC, Lam CW, Lee CH, Ma KC, Fok TF, Chan IH, et al. Reference ranges and factors affecting the human

corticotropin-releasing hormone test in preterm, very low birth weight infants. *J Clin Endocrinol Metab* 2002;**87**:4621—8.
22. Niwa F, Kawai M, Kanazawa H, Iwanaga K, Matsukura T, Shibata M, et al. Limited response to CRH stimulation tests at 2 weeks of age in preterm infants born at less than 30 weeks of gestational age. *Clin Endocrinol (Oxf)* 2013;**78**:724—9.
23. Waffarn F, Davis EP. Effects of antenatal corticosteroids on the hypothalamic-pituitary-adrenocortical axis of the fetus and newborn: experimental findings and clinical considerations. *Am J Obstet Gynecol* 2012;**207**:446—54.
24. Bancalari EH, Jobe AH. The respiratory course of extremely preterm infants: a dilemma for diagnosis and terminology. *J Pediatr* 2012;**161**:585—8.
25. Wallace AM, Beesley J, Thomson M, Giles CA, Ross AM, Taylor NF. Adrenal status during the first month of life in mature and premature human infants. *J Endocrinol* 1987;**112**:473—80.
26. Sulyok E, Varga F, Györy E, Jobst K, Csaba IF. Postnatal development of renal sodium handling in premature infants. *J Pediatr* 1979;**95**:787—92.
27. Rayson BM, Edelman IS. Glucocorticoid stimulation of Na-K-ATPase in superfused distal segments of kidney tubules in vitro. *Am J Physiol* 1982;**243**:F463—70.
28. Fonseca V, Brown R, Hochhauser D, Ginsburg J, Havard CW. Acute adrenal crisis precipitated by thyroxine. *Br Med J (Clin Res Ed)* 1986;**292**:1185—6.
29. Nakanishi H, Yamanaka S, Koriyama T, Shishida N, Miyagi N, Kim TJ, et al. Clinical characterization and long-term prognosis of neurological development in preterm infants with late-onset circulatory collapse. *J Perinatol* 2010;**30**:751—6.
30. Cartlidge PH, Rutter N. Serum albumin concentrations and oedema in the newborn. *Arch Dis Child* 1986;**61**:657—60.
31. Washio Y, Uchiyama A, Nakanishi H, Totsu S, Masumoto K, Kusuda S. Hemodynamic analysis in infants with late-onset circulatory collapse. *Pediatr Int* 2013;**55**:582—8.
32. Kempley ST, Murdoch E. Splanchnic haemodynamic disturbances in perinatal sepsis. *Arch Dis Child Fetal Neonatal Ed* 2000;**83**:F139—42.
33. Uchiyama A, Kusuda S, Sakuma I, Yamazaki C, Obouchi T, Tamura Y, et al. Late-onset circulatory collapse: diagnostic criteria. *J Jpn Soc Premature Newborn Med* 2007;**19**:483 [Article in Japanese].
34. Fernandez E, Schrader R, Watterberg K. Prevalence of low cortisol values in term and near-term infants with vasopressor-resistant hypotension. *J Perinatol* 2005;**25**:114—8.
35. Al Saedi S, Dean H, Dent W, Cronin C. Reference ranges for serum cortisol and 17-hydroxyprogesterone levels in preterm infants. *J Pediatr* 1995;**126**:985—7.
36. Scott SM, Watterberg KL. Effect of gestational age, postnatal age, and illness on plasma cortisol concentrations in premature infants. *Pediatr Res* 1995;**37**:112—6.
37. Masumoto K, Tagawa N, Kobayashi Y, Kusuda S. Cortisol production in preterm infants with or without late-onset adrenal insufficiency of prematurity: a prospective observational study. *Pediatr Neonatol* 2019;**60**:504—11.
38. Sari FN, Dizdar EA, Oguz SS, Andiran N, Erdeve O, Uras N, et al. Baseline and stimulated cortisol levels in preterm infants: is there any clinical relevance? *Horm Res Paediatr* 2012;**77**:12—8.
39. Iijima S, Uga N, Ohzeki T. Postnatal changes in adrenal size in very low-birth-weight infants: sonographic evaluation for the prediction of late-onset glucocorticoid-responsive circulatory collapse. *Am J Perinatol* 2010;**27**:485—91.
40. Baud O, Watterberg KL. Prophylactic postnatal corticosteroids: early hydrocortisone. *Semin Fetal Neonatal Med* 2019;**24**:202—6.
41. Lynch SK, Mullett MD, Graeber JE, Polak MJ. A comparison of albumin-bolus therapy versus normal saline-bolus therapy for hypotension in neonates. *J Perinatol* 2008;**28**:29—33.
42. Noori S, Seri I. Neonatal blood pressure support: the use of inotropes, lusitropes, and other vasopressor agents. *Clin Perinatol* 2012;**39**:221—38.
43. Seri I, Evans J. Addition of epinephrine to dopamine increases blood pressure and urine output in critically ill extremely low birthweight neonates with uncompensated shock. *Pediatr Res* 1998;**43**:194A.
44. Revollo JR, Cidlowski JA. Mechanisms generating diversity in glucocorticoid receptor signaling. *Ann N Y Acad Sci* 2009;**1179**:167—78.
45. Bourchier D, Weston PJ. Randomised trial of dopamine compared with hydrocortisone for the treatment of hypotensive very low birthweight infants. *Arch Dis Child Fetal Neonatal Ed* 1997;**76**:F174—8.
46. Efird MM, Heerens AT, Gordon PV, Bose CL, Young DA. A randomized-controlled trial of prophylactic hydrocortisone supplementation for the prevention of hypotension in extremely low birth weight infants. *J Perinatol* 2005;**25**:119—24.
47. Noori S, Friedlich P, Wong P, Ebrahimi M, Siassi B, Seri I. Hemodynamic changes after low-dosage hydrocortisone administration in vasopressor-treated preterm and term neonates. *Pediatrics* 2006;**118**:1456—66.
48. Johnson PJ. Hydrocortisone for treatment of hypotension in the newborn. *Neonatal Netw* 2015;**34**:46—51.
49. Watterberg KL. Hydrocortisone dosing for hypotension in newborn infants: less is more. *J Pediatr* 2016;**174**:23—6.
50. Peeples ES. An evaluation of hydrocortisone dosing for neonatal refractory hypotension. *J Perinatol* 2017;**37**:943—6.
51. Mass Screening Committee, Japanese Society for Pediatric Endocrinology, Japanese Society for Mass Screening, Ishii T, Anzo M, Adachi M, et al. Guidelines for diagnosis and treatment of 21-hydroxylase deficiency (2014 revision). *Clin Pediatr Endocrinol* 2015;**24**:77—105.
52. Seri I, Noori S. Diagnosis and treatment of neonatal hypotension outside the transitional period. *Early Hum Dev* 2005;**81**:405—11.
53. Kennedy KA, Cotten CM, Watterberg KL, Carlo WA. Prevention and management of bronchopulmonary dysplasia: lessons learned from the neonatal research network. *Semin Perinatol* 2016;**40**:348—55.
54. Beaulieu MJ. Vasopressin for the treatment of neonatal hypotension. *Neonatal Netw* 2013;**32**:120—4.
55. Ikegami H, Funato M, Tamai H, Wada H, Nabetani M, Nishihara M. Low-dose vasopressin infusion therapy for refractory hypotension in ELBW infants. *Pediatr Int* 2010;**52**:368—73.
56. Fukuda S, Mizuno K, Kakita H, Kato T, Hussein MH, Ito T, et al. Late circulatory dysfunction and decreased cerebral blood flow volume in infants with periventricular leukomalacia. *Brain Dev* 2008;**30**:589—94.
57. Kobayashi S, Fujimoto S, Koyama N, Fukuda S, Iwaki T, Tanaka T, et al. Late-onset circulatory dysfunction of premature infants and late-onset periventricular leukomalacia. *Pediatr Int* 2008;**50**:225—31.
58. Arima M, Tsukamoto S, Fujiwara K, Murayama M, Fujikawa K, Sonoda KH. Late-onset circulatory collapse and continuous positive airway pressure are useful predictors of treatment-requiring retinopathy of prematurity: a 9-year retrospective analysis. *Sci Rep* 2017;**7**:3904.
59. Ng PC, Kwok AK, Lee CH, Tam BS, Lam CW, Ma KC, et al. Early pituitary-adrenal responses and retinopathy of prematurity in very low birth weight infants. *Pediatr Res* 2004;**55**:114—9.
60. Catenacci M, Miyagi S, Wickremasinghe AC, Lucas SS, de Alba Campomanes AG, Good WV, et al. Dopamine-resistant hypotension and severe retinopathy of prematurity. *J Pediatr* 2013;**163**:400—5.