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Original Article

Postnatal hydrocortisone therapy for the treatment of bronchopulmonary dysplasia in very low birth weight infants

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Abstract

Aim: Corticosteroids are widely used to prevent and treat bronchopulmonary dysplasia (BPD) due to their strong anti-inflammatory effects. We aim to evaluate the outcomes of late onset systemic hydrocortisone (HC) therapy in very low birth weight infants with BPD.

Material and Methods: The medical records of 706 preterm infants with gestational age ≤ 30 weeks over a 4-year period were retrospectively reviewed. Infants who required invasive/noninvasive respiratory support or ≥ 30% oxygen due to BPD and were treated with HC after the third postnatal week were included. The infants were divided into 3 groups according to respiratory support at the beginning of the HC treatment: mechanical ventilation (MV), noninvasive ventilation (NIV), and free oxygen.

Results: Seventy-six (11.9%) infants in our cohort received HC therapy. In the MV group, 83.3% of the infants were successfully extubated after a median of 4 days (interquartile range [IQR], 2-8 days). In the NIV group, 83.9% of the infants required no longer respiratory support after a median of 6 days (IQR, 3-16 days). In the free oxygen group, none of the infants needed supplemental oxygen after a median of 8 days (IQR, 6-12 days).

Conclusion: Late HC therapy facilitates extubating without adverse short-term effects, reduces the need of invasive and noninvasive ventilation, and facilitates discharge without supplemental oxygen.

Keywords: Bronchopulmonary dysplasia; hydrocortisone; postnatal steroids; premature

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is a common respiratory disorder which is characterized by inflammation (1-3). Corticosteroids, which are commonly used in prevention and treatment of BPD due to their anti-inflammatory properties, improve lung function and facilitate extubating (4-6).

Systemic corticosteroids, particularly dexamethasone, have been shown to decrease the incidence of BPD and death in preterm infants being supported with invasive ventilation (7,8). Following studies demonstrated that early postnatal systemic dexamethasone therapy was associated with the risk of abnormal neurological development, hydrocortisone (HC) has started to be used more frequently (9-12). The results of an animal study indicated that, unlike dexamethasone, HC had no adverse effect on brain (13). It has been shown that HC therapy at the end of first postnatal week was as effective as dexamethasone in reducing death or BPD, without increasing the risk of unfavorable neurological outcomes (14,15). There are also studies that showed no increase in survival without BPD or extubation rates with early low-dose HC therapy (16,17). However, the recent PREMILOC study demonstrated that early low-dose HC increased survival without BPD in extremely low birth weight (ELBW) infants with no significant adverse neurodevelopmental effects at two years of age (18,19).

Although postnatal systemic corticosteroid therapy is not recommended as preferred treatment or standard

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practice for preterm infants who are still ventilator-dependent after the first week of life (20,21), recent publications indicate that corticosteroids are still used at high doses (11,12,22,23). Studies in literature have usually focused on steroid use in patients who are dependent on mechanical ventilation or as early prophylaxis; however, there have been no studies investigating steroid use in infants requiring prolonged noninvasive ventilation and oxygen support at high concentrations.

The aim of this study was to evaluate the short-term outcomes of late onset HC treatment in very low birth weight infants who required invasive or noninvasive ventilation support or supplemental oxygen due to BPD.

MATERIAL and METHODS

Study Population

In this retrospective cohort study, we reviewed the medical records of 706 preterm infants of gestational age ≤ 30 weeks who were admitted to our level III neonatal intensive care unit between January 2013 andDecember 2016 (Figure 1). Ethical approval for this study was obtained from the research ethics committee of Zekai Tahir Burak Hospital.

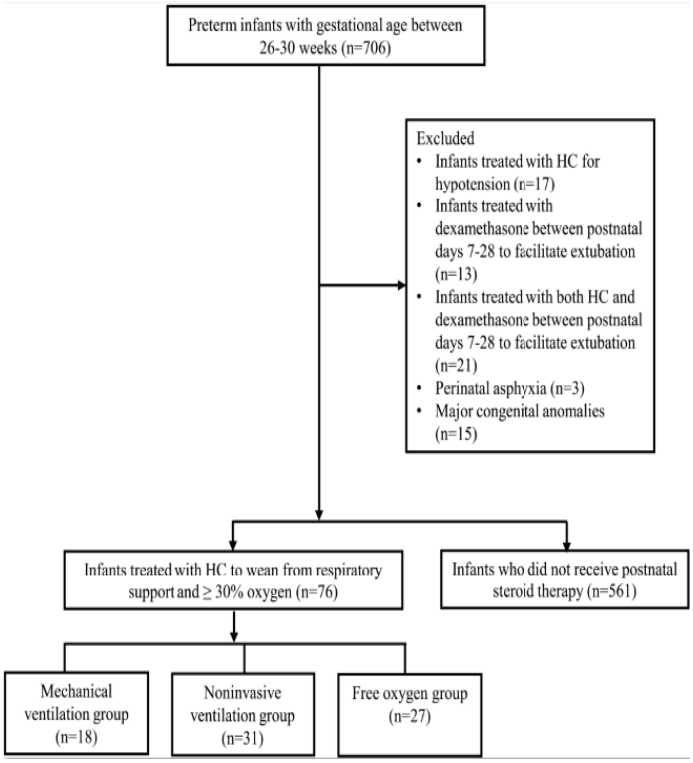

Figure 1. Study Population HC, Hydrocortisone

Inclusion criteria were

- Gestation age ≤ 30 weeks
- To receive HC treatment after postnatal 3rd week of life due to need of prolonged invasive/noninvasive respiratory support and/or requirement of >30% oxygen, in the absence of any underlying infection or heart disease

Exclusion criteria were:

- To receive HC treatment for hypotension,
- To receive dexamethasone or both dexamethasone and HC between postnatal 7-28 days to improve lung function and respiratory condition,
- Perinatal asphyxia,
- Major congenital anomalies.

The infants were divided into 3 groups according to respiratory support at the beginning of HC treatment: mechanical ventilation (MV), noninvasive ventilation (NIV), and free oxygen.

Study Protocol

Patients' maternal and fetal demographic characteristics, clinical outcomes, respiratory data, and length of hospital stay were recorded. Gestational age was calculated according to the date of the last menstrual period and the crown-rump length in the first trimester ultrasound. In our unit, caffeine therapy is initiated within the first 3 hours of life for all preterm infants with a birth weight less than 1,250 g. For infants requiring respiratory support and supplemental oxygen, our ventilation policy is to adjust respiratory device parameters and FiO2 level to achieve a target oxygen saturation level of 90-95%.

The dosing regimen for oral HC therapy was 5 mg/kg/day divided into 4 doses per day for the first 7 days, followed by 3.75 mg/kg/day divided into 3 doses per day for the next 5 days, and then decreased by 1.25 mg/kg/day once every 5 days for a cumulative dose of 72.5 mg/kg over a total of 22 days (14,24). We recorded the day HC therapy was initiated, number of days given, cumulative dose, side effects, discontinuation of treatment and reason, respiratory support after HC therapy, and last day of supplemental oxygen requirement.

Primary and secondary outcomes

Our primary outcome was moderate to severe BPD at 36 weeks of postmenstrual age (PMA).

Secondary outcomes were FiO2 level at 36 weeks PMA; duration of mechanical ventilation, noninvasive ventilation, and supplemental oxygen requirement; duration of hospitalization; and oxygen requirement at discharge.

Definitions

BPD at 36 weeks PMA was assessed according to the NICHD Consensus Statement using the severity classification proposed by Jobe et al. (3) when necessary, the oxygen reduction test was conducted as described by Wash et al. (25). Moderate BPD was defined as the need of oxygen for ≥28 days, as well as treatment with <30% oxygen at 36 weeks of postconceptional age. Severe BPD was defined as needing oxygen for the first 28 days and oxygen >30% and continuous positive airway pressure (CPAP) or mechanical ventilation at 36 weeks of postconceptional age (3). Echocardiography was performed routinely for patent ductus arteriosus (PDA) at postnatal age of 48-96 h (26). Cranial ultrasonography was performed on days 3, 7, and 28 and at 36 weeks of gestational age. We assessed the infants for intraventricular hemorrhage

using the Papile classification system (27), for necrotizing enterocolitis with the modified Bell's classification system (28), and for retinopathy of prematurity requiring laser treatment based on the criteria of the American Academy of Pediatrics, American Academy of Ophthalmology, and the American Association for Pediatric Ophthalmology and Strabismus (29).

Statistical analysis

Statistical analyses were performed with SPSS Statistics for Windows, Version 22 (IBM SPSS Statistics, Armonk, NY, USA). Categorical variables were given as frequencies and percentages. Continuous variables were expressed as means [standard deviations (SD)] or medians [interquartile ranges (IQR)], according to the distribution of the variables, as appropriate. Comparison of related variables were performed by using 2-related samples test. A p value less than .05 was considered statistically significant for all analyses.

RESULTS

A total of 76 (11.9%) infants in the study population were treated with HC. This group accounted for 56.6% of all preterm infants who received antenatal steroids, and their median gestational age was 27 weeks (26-28 weeks) and mean birth weight was 946±196 g. The demographic characteristics of the three groups are summarized in Table 1.

Table 1. Demographic characteristics of the study group

	MV (n=18)	NIV (n=31)	Free O_2 (n=27)
Gestational age, weeks*	26.6 (26-27.4)	27.2 (26-28)	27.4 (26.4-28.3)
Birth weight, g†	864±170	956±208	989±187
Male, n (%)	7 (38.9)	17 (54.8)	20 (74.1)
APGAR score at 5 min*	6.5 (6-8)	7 (6-8)	7 (5-7)
Antenatal steroid therapy, n (%)	11 (61.1)	15 (48.4)	17 (63)
Preeclampsia, n (%)	3 (16.7)	6 (19.4)	5 (18.5)
Gestational diabetes, n (%)	1 (5.6)	-	3 (11.1)
Cesarean delivery, n (%)	16 (88.9)	28 (90.3)	20 (74.1)
Clinical chorioamnionitis, n (%)	4 (22.2)	5 (16.1)	4 (14.8)
SGA, n (%)	2 (11.1)	5 (16.1)	4 (14.8)
Multiple pregnancy, n (%)	-	8 (25.8)	3 (11.1)
CRIB score*	4.5 (3-6.2)	4 (3-7)	4 (2-5)

*Median (interquartile range) †Mean ± standard deviation
MV, Mechanical ventilation; NIV, Noninvasive ventilation; O2, Oxygen; CRIB, Clinical Risk Index for Babies; SGA, Small for gestational age

The proportion of infants with moderate to severe BPD at 36 weeks PMA was 48.4% in the MV group, 61.1% in the NIV group, and 44.6% in the free oxygen group (Table 2). First day of HC therapy was postnatal (median) 34th day of life in the groups requiring MV and NIV at the beginning of the treatment, and postnatal 55th day in the free oxygen group. Fifteen (83.3%) of the infants in the MV group were extubated after HC treatment, while extubation was not possible for 3 infants (16.7%). In the NIV group, 26 infants (83.9%) no longer required respiratory support after HC therapy. In the free oxygen group, 15 (55.6%) infants did not require any oxygen after HC treatment (Table 2). Secondary outcomes are summarized in Table 2. FiO2 levels decreased significantly in all groups after initiation of HC therapy (Figure 2).

The preterm morbidities are summarized in Table 3.

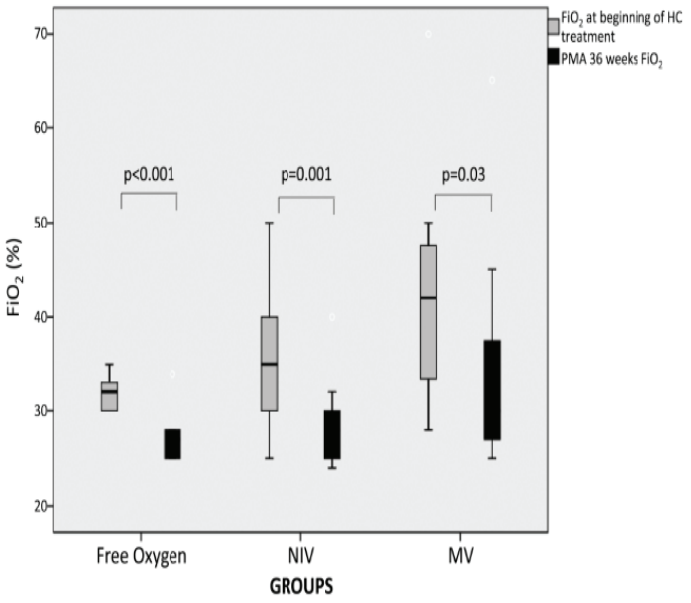

Figure 2. Free oxygen, NIV and MV groups, day of HC treatment initiation and PMA 36th week FiO_2 HC, Hydrocortisone; MV, Mechanical ventilation; NIV, Noninvasive ventilation; O_2, Oxygen; PMA, postmenstrual age. There was a significant decrease in FiO_2 at 36 weeks of PMA in all three groups

There was no mortality among the infants treated with HC.

Three (16.7%) infants in the MV group and 2 (6.5%) infants in the NIV group received a second course of HC.

Four infants (5.2%) developed infection, and hyperglycemia and hypertension were each observed in 1 infant (1.3%) as side effects of HC.

Table 2. Primary and secondary outcomes and specifics of hydrocortisone therapy

	MV (n=18)	NIV (n=31)	Free O_2 (n=27)
Moderate/severe BPD, n (%)	11 (61.1)	15 (48.4)	12 (44.6)
FiO2 at 36 weeks PMA*	30 (27-39)	28 (25-30)	27 (25-28)
Discharge with oxygen, n (%)	1 (5.6)	1 (3.2)	-
Duration of hospitalization, days†	113.1±39.4	96.6±23.6	83.5±16.6
PMA at discharge, weeks†	43.2±5.8	41.6±3.6	39±2
Pre-HC/total free O2 duration, days*	0 (0-0)	3 (0-15)	26 (18-31)
	18.5 (12.5-30.5)	24 (18-38)	34 (24-42)
Pre-HC/total NIV duration, days*	8 (2-21)	18 (13-23)	18 (9-24)
	18.5 (9.7-39.2)	22 (20-36)	20 (13-24)
Pre-HC/total MV duration, days*	23.5 (19-30)	8 (1-20)	6 (0-7)
	29.5 (23.7-44.5)	9 (1-21)	6 (1-7)
Postnatal age at start of HC, day*	34 (27-48.5)	34 (30-43)	55 (45-64)
Duration of HC, days*	22 (22-22)	22 (21-22)	19 (12-22)
Cumulative HC dose (mg/kg)*	72.5 (72.5-72.5)	72.5 (71.5-72.5)	69 (53.7-72.5)
Respiratory support at 36 weeks PMA, n (%)			
None	7 (38.9)	16 (51.6)	15 (55.6)
O2	3 (16.7)	10 (32.3)	11 (40.7)
NIV	5 (27.8)	5 (16.1)	1 (3.7)
MV	3 (16.7)	-	-

* Median (interquartile range) † Mean ± standard deviation
BPD, Bronchopulmonary dysplasia; FiO2, Inspiratory oxygen fraction; HC, Hydrocortisone; MV, Mechanical ventilation; NIV, Noninvasive ventilation; O2, Oxygen; PMA, postmenstrual age

Table 3. Preterm morbidities and clinical features of the study groups

	MV (n=18)	NIV (n=31)	Free O_2 (n=27)
Surfactant treatment, n (%)	17 (94.4)	28 (90.3)	19 (70.4)
PDA requiring medication, n (%)	11 (61.1)	19 (61.3)	15 (55.6)
Early-onset neonatal sepsis, n (%)	4 (22.2)	5 (16.1)	5 (18.5)
Late-onset neonatal sepsis, n (%)	17 (94.4)	25 (80.6)	19 (70.4)
Necrotising enterocolitis ≥ stage II, n (%)	-	-	2 (7.4)
Intraventricular hemorrhage > grade II, n (%)	4 (22.2)	7 (22.6)	7 (25.9)
Cystic PVL*	3 (16.7)	5 (16.1)	3 (11.1)
ROP, n (%)*	9 (50)	13 (41.9)	5 (18.5)
FiO2 at postnatal day 28*	35.5 (30-41)	30 (25-35)	26 (25-30)
Weight at discharge, g†	2869±829	2617±577	2708±755

*Median (interquartile range) †Mean ± standard deviation
MV, Mechanical ventilation; NIV, Noninvasive ventilation; O2, Oxygen; PDA, Patent ductus arteriosus; PVL, Periventricular leukomalacia; ROP, Retinopathy of prematurity

DISCUSSION

This study showed that late HC therapy in infants requiring invasive or noninvasive respiratory support after the third week of life reduced the need for respiratory support and supplemental oxygen at 36 weeks PMA, thus reducing the incidence of moderate to severe BPD. HC therapy was also found to facilitate discharge without oxygen in patients who has required more than 30% supplemental oxygen

In a systematic review of prophylactic early low-dose HC treatment, there was little evidence to support the use of HC to prevent BPD; there was no reduction in important outcomes such as mortality, BPD rate, and home oxygen dependence (17). However, the recent PREMILOC study demonstrated that prophylactic HC administered within the first 24 hours of life and at a cumulative dose of 8.5 mg/kg increased survival without BPD at postnatal week 36 (18). In previous studies of HC therapy in preterm infants who were ventilator-dependent after the second postnatal week, Renault et al. (30) showed that a cumulative dose of 27.2 mg/kg significantly reduced BPD and Ben Said et al. (31) determined that a cumulative dose of 22 mg/kg facilitated extubation similarly to betamethasone. In contrast, Nehal et al. (32) reported no significant difference in survival without BPD at 36 weeks PMA with a cumulative dose of 17 mg/kg. Two studies with median cumulative HC doses of 72.5 mg/kg and 56.9 mg/kg also demonstrated beneficial effects on respiratory outcomes such as facilitating extubation and reducing the need for supplemental oxygen (14,33). In the present study, HC therapy was initiated later than in other studies and the cumulative dose was 72.5 mg/kg. We observed that this treatment substantially facilitated extubation and reduced the need for high-concentration supplemental oxygen in our patients.

The preterm infants in our cohort who received HC treatment had low rates of antenatal steroid use, low gestational age and birth weight, and high incidence of morbidities of prematurity. Moreover, because these were infants who could not be extubated and required positive pressure ventilation for longer periods, they could not be weaned from invasive and noninvasive respiratory support and high-concentration oxygen in the late postnatal period. As a result of HC therapy started at a median of 32 weeks PMA, about 84% of the infants in the invasive and noninvasive ventilation groups no longer required positive pressure ventilation within 4-5 days. Various other studies also reported that HC therapy in ventilator-dependent preterm infants led to high extubating success rates in their study groups in 4-7 days (8,14,31,33). In our free oxygen group, 55% of the infants did not require additional oxygen after 1 week. Two studies of HC therapy showed that FiO2 levels decreased significantly during the first 3 days (14,33). We also observed a significant decrease in FiO2 level in all three groups after HC treatment. The main reason for the initiation of hydrocortisone in premature infants with free oxygen requirement in our study group is the high resistance of the families to discharge with oxygen. It is conceivable that these improvements in respiratory outcomes may occur over time even without HC therapy. However, the treatment group in our study consisted of infants with moderate and severe BPD and the rapid pulmonary improvement brought about by HC avoided respiratory support dependence and enabled 97.4% of the infants to be discharged with no supplemental oxygen. This improvement might also contribute to long-term neurodevelopmental outcomes in preterm infants with such severe clinical conditions.

A Cochrane meta-analysis reported that late steroid treatment increased the risk of short-term side effects such as gastrointestinal hemorrhage, hyperglycemia, hypertension, and hypertrophic cardiomyopathy (8). In another study, high-dose HC was associated with higher incidence of hypertension, but not hyperglycemia (14). Another study showed an increase in the incidence of hyperglycemia but no difference in terms of hypertension during median dose HC therapy. (31) In the present study, HC therapy was discontinued in 4 infants (5.2%) due to sepsis, and hyperglycemia and hypertension severe enough to require treatment cessation each developed in 1 infant (1.3%). No other side effects were observed. Previous studies involving high cumulative doses of HC showed no increase in the incidence of cerebral palsy at 2 years of age and no adverse impact on neurodevelopmental outcomes or performance in school at 5-7 years (14,33,34). An evaluation of the neurodevelopmental outcomes of our patients at 2 years and school age will be published in a latter report.

The main limitation of our study is that it was not a randomized controlled study, and because of its retrospective nature, we could not include a control group of infants with comparably severe clinical condition to the treatment group but did not receive HC. Another limitation of our study was that families showed extreme resistance to discharge with respiratory support.

CONCLUSION

In conclusion, our study demonstrates that late HC therapy for VLBW infants with prolonged need for respiratory support and high-concentration oxygen facilitates extubation without adverse short-term effects and reduces the need for invasive and noninvasive ventilation and supplemental oxygen, thus enabling more patients to be discharged without oxygen. Larger, randomized controlled trials are needed to further evaluate HC therapy for BPD.

Competing interests: The authors found that the conflict of interest did not fully coincide.

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Ethical approval: Zekai Tahir Burak Maternity Education and Research Hospital ethical committee approved this study.

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REFERENCES

1. Davis PG, Thorpe K, Roberts R, et al. Trial Indomethacin Prophylaxis in Preterms Investigators: Evaluating 'old' definitions for the 'new' bronchopulmonary dysplasia. J Pediatr 2002;140:555-60.
2. Hentschel J, Berger TM, Tschopp A, et al. Population-based study of bronchopulmonary dysplasia in very low birth weight infants in Switzerland. Eur J Pediatr 2005;164:292-7.
3. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med 2001;163:1723-9.
4. WatterbergK. Evidence-based neonatal pharmacotherapy: postnatal corticosteroids. Clin Perinatol 2012;39:47-59.
5. Jobe AH. Postnatal corticosteroids for bronchopulmonary dysplasia. Clin Perinatol 2009; 36:177-88.
6. Aschner JL, Bancalari EH, McEvoy CT. Can We Prevent Bronchopulmonary Dysplasia? J Pediatr 2017;189:26-30.
7. Doyle LW, Ehrenkranz RA, Halliday HL. Early (<8 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants. Cochrane Database Syst Rev 2014;5:CD001146.
8. Doyle LW, Ehrenkranz RA, Halliday HL. Late (>7 days) postnatal corticosteroids for chronic lung disease in preterm infants. Cochrane Database Syst Rev 2014;5:CD001145.
9. Yeh TF, Lin YJ, Huang CC, et al. Early dexamethasone therapy in preterm infants: a follow-up study. Pediatrics 1998;1015:7.
10. O'Shea TM, Kothadia JM, Klinepeter KL, et al. Randomized placebo-controlled trial of a 42-day tapering course of dexamethasone to reduce the duration of ventilator dependency in very low birth weight infants: outcome of study participants at 1-year adjusted age. Pediatrics 1999;104:15-21.
11. Walsh MC, Yao Q, Horbar JD, et al. Changes in the use of postnatal steroids for bronchopulmonary dysplasia in 3 large neonatal networks. Pediatrics 2006;118:1328-35.
12. Yoder BA, Harrison M, Clark RH. Time-related changes in steroid use and bronchopulmonary dysplasia in preterm infants. Pediatrics 2009;124:673-9.
13. Huang CC, Lin HR, Liang YC, et al. Effects of neonatal corticosteroid treatment on hippocampal synaptic function. Pediatric Research 2007;62:267-70.
14. van der Heide-Jalving M, Kamphuis PJ, van der Lann MJ, et al. Short- and long-term effects of neonatal glucocorticoid therapy: is hydrocortisone an alternative to dexamethasone? Acta Paediatr 2003;92:827-35.
15. Rademaker KJ, de Vries LS, Uiterwaal CS, et al. Postnatal hydrocortisone treatment for chronic lung disease in the preterm newborn and long-term neurodevelopmental follow-up. Arch Dis Child Fetal Neonatal Ed 2008;93:F58–63.
16. Watterberg KL, Gerdes JS, Cole CH, et al. Prophylaxis of early adrenal insufficiency to prevent bronchopulmonary dysplasia: a multicenter trial. Pediatrics 2004;114:1649-57.
17. Doyle LW, Ehrenkranz RA, Halliday HL. Postnatal hydrocortisone for preventing or treating bronchopulmonary dysplasia in preterm infants: a systematic review. Neonatology 2010;98:111-7.
18. Baud O, Maury L, Lebail F, et al. Effect of early low-dose hydrocortisone on survival without bronchopulmonary dysplasia in extremely preterminfants (PREMILOC): a doubleblind, placebo-controlled, multicentre, randomised trial. Lancet 2016;387:1827-36.
19. Baud O, Trousson C, Biran V, et al. Association between early low-dose hydrocortisone therapy in extremely preterm neonates and neurodevelopmental outcomes at 2 years of age. JAMA 2017;317:1329-37.
20. Onland W, De Jaegere AP, Offringa M, et al. Systemic corticosteroid regimens for prevention of bronchopulmonary dysplasia in preterm infants. Cochrane Database Syst Rev 2017;1:CD010941.
21. Halliday HL. Update on Postnatal Steroids. Neonatology 2017;111:415-22.
22. Virkud YV, Hornik CP, Benjamin DK, et al.Respiratory support for very low birth weight infants receiving dexamethasone. J Pediatr 2017;183:26-30.
23. Nuytten A, Behal H, Duhamel A, et al; EPICE Research Group: Evidence-based neonatal unit practices and determinants of postnatal corticosteroid-use in preterm births below 30 weeks GA in Europe: a population-based cohort study. PLoS One 2017;12:0170234.
24. Onland W, Offringa M, Cools F, et al. Systemic Hydrocortisone To Prevent Bronchopulmonary Dysplasia in preterm infants (the SToP-BPD study); a multicenter randomized placebo controlled trial. BMC Pediatr 2011;11:102.
25. Walsh MC, Wilson-Costello D, Zadell A, et al. Safety, reliability, and validity of a physiologic definition of bronchopulmonary dysplasia. J Perinatol 2003;23:451-6.
26. Oncel MY, Yurttutan S, Erdeve O, et al. Oral paracetamol versus oral ibuprofen in the management of patent ductus arteriosus in preterm infants: a randomized controlled trial. J Pediatr 2014;164:510-4.
27. Papile LA, Burstein J, Burstein R, et al. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr 1978;92:529-33.
28. Bell MJ, Ternberg JL, Feigin RD, et al. Neonatal necrotizing enterocolitis: therapeutic decisions based

upon clinical staging. Ann Surg 1978;187:1-7.
29. Section on Ophthalmology American Academy of Pediatrics, American Academy of Ophthalmology, American Association for Pediatric Ophthalmology and Strabismus. Screening examination of premature infants for retinopathy of prematurity. Pediatrics 2006;117:572-576.
30. Renault A, Patkaï J, Dassieu G, et al. Hydrocortisone use in ventilated extremely preterm infants decreased bronchopulmonary dysplasia with no effects on neurodevelopment after two years. Acta Paediatr 2016;105:1047-55.
31. Ben Said M, Hays S, Loys CM, et al. Postnatal steroids in extremely low birth weight infants: betamethasone or hydrocortisone? Acta Paediatr 2013;102:689-94.
32. Parikh NA, Kennedy KA, Lasky RE, et al. Pilot randomized trial of hydrocortisone in ventilator-dependent extremely preterm infants: effects on regional brain volumes. J Pediatr 2013;162:685-90.
33. de Jong SE, Groenendaal F, van Bel F, et al. Pulmonary effects of neonatal hydrocortisone treatment in ventilator-dependent preterm infants. Int J Pediatr 2011;783893:7.
34. Rademaker KJ, Uiterwaal CS, Groenendaal F, et al. Neonatal hydrocortisone treatment: neurodevelopmental outcome and MRI at school age in preterm-born children. J Pediatr 2007;150:351-7.