Congenital diaphragmatic hernia: experience of 14 years

G. ROCHA [1], M. J. BAPTISTA [2], J. CORREIA-PINTO [3], H. GUIMARÃES [1]

Aim. **Over the last two decades, new therapies have emerged for the management of congenital diaphragmatic hernia (CDH). The aim of this paper was to review our experience in the management of newborns diagnosed with CDH over a 14-year period.**

Methods. **Review of maternal and infant medical records, 1997-2010.**

Results. **Eighty newborns with CDH; 21 (26%) were preterm and 28 (35%) of low birthweight (<2500 g), including 3 (4%) of very low birthweight (< 1500 g). Prenatal diagnosis was made in 53 (66%) cases. The location of the hernia was: left side 48 (90.5%); right 4 (7.5%); bilateral 1 (1%). Corrective surgery was performed in 58 (73%) patients. High frequency oscillatory ventilation was used in 10 (12.5%), inhaled nitric oxide in 18 (22.5%), sildenafil in 15 (18.7%) and extracorporeal membrane oxygenation in 1 (1%). The overall survival was 49% (N.=39). Since 2003, the overall survival raised to 64%. The survival rate of the appropriate for gestational age term newborns without other congenital/chromosomal anomaly or hydrops fetalis was 67% (24/36).**

Conclusion. **Our survival rate for congenital diaphragmatic hernia has improved over the last 14 years, associated to the use of new therapies, such as high-frequency oscillation ventilation (HFOV), inhaled nitric oxide and sildenafil.**

Key words: **Congenital diaphragmatic hernia - Therapeutics - Survival rate.**

Corresponding author: G. Rocha, Service of de Neonatoly, Departament of Pediatrics São João Hospital, Piso 2, Alameda Prof. Hernâni Monteiro, 4202 – 451 Porto, Portugal.
E-mail: gusrocha@oninet.pt

[1]Division of Neonatology, Department of Pediatrics Faculty of Medicine of Porto University Hospital de São João, Porto, Portugal
[2]Division of Pediatric Cardiology, Department of Pediatrics School of Health Sciences of Minho University Hospital de São João, Porto, Portugal
[3]Division of Pediatric Surgery, Department of Pediatrics Hospital de São João, Porto, Portugal

Over the course of the past two decades, along with the increase in prenatal detection and transfer to tertiary institutions for delivery and treatment, new therapies have emerged for the management of congenital diaphragmatic hernia (CDH), including delayed operative repair,[1, 2-4] inhaled nitric oxide (INO),[5] high-frequency oscillation ventilation (HFOV),[4, 6, 7] gentle ventilation with permissive hypercapnea,[1, 2, 3, 8] and extracorporeal membrane oxygenation (ECMO).[3, 4, 9, 10] Coincidently, with these technological advances the in-hospital survival of CDH patients has improved to over 80% in some centers.[1, 8, 10-13] A standardized postnatal management of infants with CDH, the CDH EURO Consortium Consensus, has been proposed in 2010.[14]

This study was undertaken in order to review our experience in the management of newborns diagnosed with CDH over a 14-year period, before the publication of the CDH EURO Consortium Consensus.

Materials and methods

Cases of CDH were identified in our database, a tertiary referral centre for neonatal surgery. All neonates diagnosed with CDH from January 1997 to December 2010 were included. Neonates with diaphragmatic eventration were not included in the study.

Data were obtained from review of maternal and infant medical records, including demographic characteristics, prenatal diagnosis, obstetric management, place of birth, method of delivery, resuscitation and Apgar scores, presence of associated anomalies, side of defect and contents of hernia, evaluation of pulmonary hypertension, use of INO and sildenafil, timing of surgical repair, preoperative and acute postoperative complications, duration and methods of mechanical ventilation, oxygen requirement, total parenteral nutrition, use of paralysis, inotropic support, hospital stay and postmortem findings. Fetal lung-to-head ratio and ultrasonographic assessment of the degree of pulmonary hypoplasia were not undertaken routinely during the study period.

Treatment of infants with CDH included elective intubation, sedation with or without paralysis and ventilation according to clinical criteria. Permissive hypercapnea was routinely practiced. HFOV was available from 1999 and was used as a rescue modality in infants with refractory hypoxia and/or hypercapnea. INO (20 ppm) was routinely used from 2003 after echocardiography and an oxygenation index (mean airway pressure x fraction of inspired oxygen x 100 / partial arterial pressure of oxygen) over 20. Sildenafil has been used in infants with persistent pulmonary hypertension refractory to INO. Since 2003 we have routinely used a total daily water intake of 80 ml/kg (until start enteral feeds) along with a perfusion of dopamine 5 mcg/kg/min (until after surgery). A perfusion of dobutamine (5 mcg/kg/min) was started if signs of myocardial dysfunction were present at echocardiographic evaluation. Higher doses of dopamine and dobutamine were used according to clinical criteria. Routinely, all CDH patients performed echocardiography in order to detect associated congenital heart disease and evaluate the presence and significance of pulmonary hypertension. Pulmonary artery pressure estimation was based on the gradient between right ventricle and atrium, through tricuspid regurgitation, assuming the right atrium pressure as 15 mmHg (estimated pulmonary artery pressure = right ventricle to right atrium gradient + 15 mmHg). Pulmonary hypertension was stratified as mild if estimated pulmonary artery pressure was less than 40 mmHg, moderate if between 40 and 60 mmHg, and severe if higher than 60 mmHg. Additionally, the presence of right-to-left shunt at ductus arteriosus or foramen ovale was a criterion of severity of pulmonary hypertension. A policy of delayed surgery after preoperative stabilization was practiced throughout the study period. The size of the diaphragmatic defect was not determined. Data on surgical aspects such as closure of diaphragm or prosthesis use were incomplete for a significant number of patients, and were not used in this analysis. ECMO was used for the first time in one patient.

Statistical analysis

Categorical variables were compared through Chi-square or the exact Fisher´s test. The Mann-Whitney test was used to compare two independent samples. A logistic regression method was used to assess adjusted odds ratio.

Results

A total of 80 newborns with CDH were treated at our institution during the considered period. The demographics of the patient population are reported in Table I. There were 21 (26%) preterm newborns and 28 (35%) of low birthweight (<2500 g), including three (4%) of very low birthweight (<1500 g).

Prenatal diagnosis of CDH was made in 53 (66%) cases, as detailed in Table II. A case of CDH associated to a cystic hygroma of the neck did not present any other

TABLE I.—*Characteristics of the studied population.*

Patients, N. (%)	80 (100)
Male, N. (%)	41 (51)
Female, N. (%)	39 (49)
Singleton, N. (%)	78 (98)
Multiple, N. (%)	2 (2)
Birthweight (g), median (min – max)	2735 (880-3770)
1500-2500 g, N. (%)	25 (31)
<1500 g, N. (%)	3 (4)
IUGR, N. (%)	2 (3)
Gestational age (weeks), median (min – max)	38 (28- 41)
Preterm (<37 weeks), N. (%)	21 (26)
Inborn, N. (%)	58 (73)
Outborn, N. (%)	22 (27)
Prenatal diagnosis, N. (%)	53 (66)
Postnatal diagnosis, N. (%)	27 (34)
C-section, N. (%)	50 (63)

IUGR: intrauterine growth restriction

TABLE II.—*Prenatal diagnosis (N.=53).*

Side of DH N. (%)	
Left side, N. (%)	48 (90.5)
Right side, N. (%)	4 (7.5)
Bilateral, N. (%)	1 (2%)
Gestational age at PD (weeks), median (min – max)	26 (19-38)
Referred to prenatal consultation, N. (%)	33 (62)
Polyhydramnios, N. (%)	18 (34)
Chromosomal anomaly (amniotic fluid study), N. (%)	2 (3.7)
45,X0 N. (%)	1 (1.8)
47,xx,+i(9) (pter-p10::p10-pter) ish i(9) (wcp9+) N. (%)	1 (1.8)
Other major congenital anomaly, N. (%)	3 (5.6)
Esophageal atresia, N. (%)	1 (1.8)
Cystic hygroma of the neck, N. (%)	1 (1.8)
Coarctation of aorta, N. (%)	1 (1.8)
Heart disease (fetal echocardiogram), N. (%)	0 (0)
Non-immune hydrops fetalis, N. (%)	1 (1.8)
Tracheal plug, N. (%)	3 (5.6)
Elective delivery, N. (%)	42 (79.2)
Vaginal, N. (%)	9 (21.4)
C-section, N. (%)	33 (78.5)

DH: diaphragmatic hernia; PD: prenatal diagnosis

features of Fryns syndrome. Postnatal diagnosis occurred in 27 (34%) cases, in the first day of life in 22 (28%) patients, and between days 2 and 25 of life in the remaining five (6%).

The clinical characteristics of the study population are reported in Table III. Ten (12.5%) patients were admitted in spontaneous ventilation, presenting a mild res-

TABLE III.—*Clinical characteristics of the study population (N.=80).*

RESUSCITATION	
5 minute Apgar score	
<7, N. (%)	16 (20)
7-10, N. (%)	64 (80)
ADMISSION	
Mechanical ventilation, N. (%)	70 (87.5)
Spontaneous ventilation, N. (%)	10 (12.5)
Arterial blood pH	
≥7.35, N. (%)	25 (31.3)
<7.35, N. (%)	55 (68.7)
EVOLUTION	
Pulmonary hypertension	
Mild (<40 mmHg), N. (%)	19 (23.7)
Moderate (40-60 mmHg), N. (%)	27 (33.8)
Severe (>60 mmHg), N. (%)	34 (42.5)
HFOV, N. (%)	10 (12.5)
INO, N. (%)	18 (22.5)
Sildenafil, N. (%)	15 (18.7)
Inotropic support, N. (%)	42 (52.5)
ECMO, N. (%)	1 (1.2)
Need for paralysis, N. (%)	20 (25)
Preoperative pneumothorax, N. (%)	7 (8.7)
Surgery, N. (%)	58 (72.5)
Day of surgery, median (min-max)	4 (1 – 42)
Side of hernia	
Right, N. (%)	11 (13.8)
Left, N. (%)	68 (85)
Bilateral, N. (%)	1 (1.2)
Intrathoracic liver, N. (%)	22 (20)
Duration of NICU stay (days), median (min-max)	14 (1 – 167)
Postoperative complications	
Hydrothorax, N. (%)	9 (11.2)
Chylothorax, N. (%)	5 (6.2)
Sepsis, N. (%)	11 (13.8)
Pneumothorax, N. (%)	9 (11.2)
Intestinal obstruction, N. (%)	1 (1.2)
ECMO-related complications	
Hemorrhagic diatesis (hemothorax, haemopericardium, pulmonary haemorrhage), N. (%)	1 (1.2)
Deceased, N. (%)	41 (51.2)
Day 1, N. (%)	13 (31.7)
Day >1, N. (%)	29 (70.7)
Discharged, N. (%)	39 (48.7)
Oxygen at discharge, N. (%)	6 (15.3)
Home, N. (%)	22 (56.4)
Pediatric division, N. (%)	17 (43.5)

ECMO: extracorporeal membrane oxygenation; INO: inhaled nitric oxide; HFOV: high frequency oscillatory ventilation; NICU: neonatal intensive care unit.

TABLE IV.—*Comparative analysis between survivors and non-survivors.*

	Survivors (N.=39)	Non-survivors (N.=41)	P
Sex			
Male, N. (%)	25 (64)	16 (39)	0.028
Female, N. (%)	14 (36)	25 (61)	
Birthweight (g), median (min-max)	2905 (1780-3725)	2600 (880-3770)	0.022
Gestational age (weeks), Median (min-max)	38 (32 – 41)	38 (28 – 41)	0.091
Prenatal diagnosis of CDH, N. (%)	20 (51)	33 (80)	0.015
Inborn, N. (%)	23 (59)	35 (85)	0.029
Arterial pH at admission <7.35, N.(%)	19 (49)	36 (88)	0.021
Pulmonary hypertension			
Mild (<0 mmHg), N. (%)	11 (28)	8 (29)	<0.001
Moderate (40-60 mmHg), N. (%)	16 (41)	11 (27)	
Severe (>60 mmHg), N. (%)	7 (18)	27 (66)	
Systemic arterial hypotension N. (%)	7 (18)	29 (70)	<0.001
Inhaled NO, N. (%)	7 (18)	11 (27)	0.473
ECMO	0	1 (2.4)	0.001
Sildenafil N. (%)	6 (15)	9 (22)	0.546
Side of hernia			
Right, N. (%)	4 (10)	7 (17)	0.039
Left, N. (%)	35 (89)	33 (80)	
Bilateral, N. (%)	0	1 (2)	
Preoperative pneumothorax, N. (%)	0	7 (17)	0.033
Surgery, N. (%)	39 (100)	19 (46)	<0.001
Postoperative complications			
Hydrothorax, N. (%)	5 (13)	4 (10)	>0.999
Chylothorax, N. (%)	5 (13)	3 (7)	0.0654
Pneumothorax, N. (%)	3 (8)	6 (15)	0.351
Sepsis, N. (%)	7 (18)	4 (10)	0.536
Intestinal obstruction, N. (%)	1 (3)	0	0.437

ECMO: extracorporeal membrane oxygenation; NO: nitric oxide

piratory distress, before the diagnosis of CDH was done. Corrective surgery was performed in 58 (73%) patients. Twenty two (28%) patients were deceased before preoperative stabilization was achieved. Necropsy study was obtained in 17 (49%) patients and revealed a double congenital anomaly (coarctation of aorta associated to an intra-abdominal pulmonary sequestration) in one term neonate, not detected at prenatal study. Other additional findings at post-mortem study included pneumonia (six cases), meconium aspiration (three cases), fulminating sepsis (one case) and hypertensive pneumothorax (one case).

The comparative analysis of demographic and clinical data between survivors and non-survivors is reported in Table IV.

Annual trends in prenatal diagnosis, inborn patients and survival rates are reported in Table V. Survival rate has improved since 2003.

Comparison of characteristics and outcomes of infants with CDH between two epochs (1997-2002 and 2003-2010) is reported in Table VI. Survival rate was statistically different between these two epochs, even after adjustment to the variable sex (OR 3.308 [95% CI: 1.008-9.158]).

The overall survival was 49% (N.=39). Since 2003, the overall survival raised to 64%. The survival rate of the appropriate for gestational age term newborns (excluded one with intrauterine growth restriction, IUGR) without other congenital/ chromosomal anomaly or hydrops fetalis was 67% (24/36).

Discussion

The mortality rate associated with CDH varies widely between centres and remains relatively high, despite the widespread im-

TABLE V.—*Annual trends in prenatal diagnosis, inborn patients and survival.*

Year	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
N. patients	8	5	6	8	5	1	9	5	7	8	3	5	4	6
PD N. (%)	5 (63)	2 (40)	4 (67)	6 (75)	4 (80)	1 (100)	5 (56)	4 (80)	4 (57)	7 (88)	3 (100)	4 (80)	0	4 (67)
Inborn N. (%)	6 (75)	3 (60)	4 (67)	7 (88)	4 (80)	1 (100)	5 (56)	4 (80)	4 (57)	8 (100)	3 (100)	4 (80)	0	4 (67)
Survival N. (%)	2 (25)	2 (40)	1 (17)	3 (38)	1 (29)	0 (0)	5 (56)	5 (100)	4 (57)	3 (38)	2 (67)	4 (80)	4 (100)	3 (50)

PN: prenatal diagnosis.

TABLE VI.—*Comparison of characteristics and outcomes of infants with CDH between two epochs (1997-2002 and 2003-2010).*

	1997-2002 (N.=33)	2003-2010 (N.=47)	P
Gender			
Male, N. (%)	12 (36)	29 (62)	0.056
Female, N. (%)	21 (64)	18 (38)	
Gestational age (weeks)			
Median (min – max)	38 (28-41)	38 (29-41)	0.732
Birthweight (g)			
Median (min – max)	2600 (880-3770)	2810 (1335-3725)	0.154
Prenatal diagnosis N. (%)	22 (67)	31 (66)	0.899
Inborn N. (%)	25 (76)	33 (69)	0.836
Other major congenital anomaly N. (%)	3 (9)	1 (2)	0.035
Chromosomal anomaly N. (%)	2 (6)	0	0.493
Non-immune hydrops fetalis N. (%)	1 (3)	0	>0.999
IUGR N. (%)	0	1 (2)	0.432
Survival (%)	9 (27.2)	30 (63.8)	0.016

IUGR: intrauterine growth restriction.

plementation of new therapeutic modalities. Experienced referral centres with ECMO describe that a large proportion of infants can be saved.[15, 16] The overall survival rate for liveborn infants remains at about 60% to 80%.[12] Our survival rate corresponds to these figures.

The optimal management of CDH remains unsolved.[12, 16, 17] A standardized postnatal management of infants with CDH, the CDH EURO Consortium Consensus, has been proposed in 2010.[14] Use of a standardized protocol may contribute to more valid comparisons of patient data in multicentre studies and identification of areas for further research.[18] Different patients have different degrees of pulmonary hypertension. Geggel *et al.* showed hypoplastic lung not only in the ipsilateral but also in the contralateral lung of infants born with CDH.[18]

Many new therapeutic modalities used in infants with this problem have been implemented without properly controlled studies.[19] It remains uncertain, and cannot be recommended at this time, that antenatal corticosteroids should be provided beyond 34 weeks of gestation in pregnancies complicated with CDH in an attempt to "mature" the fetal lung.[17, 19] Whereas there may be potential advantages of planning the timing of delivery of a fetus known to have a CDH, there are no controlled trials to support either scheduling these deliveries electively or opting for a caesarean section versus the vaginal route.[20] In this study, we verified at post-mortem study that three of the deceased infants were born by vaginal route and presented a significant meconium aspiration. This may be in favour of a C-section. Notwithstanding, given that the postnatal management of these infants often involves utilization of invasive therapies, such INO, HFOV, and ECMO, whenever possible, deliveries of these infants should occur in a centre experienced in the use of these modalities. Further support for these recommendations stems from reports of increased survival for infants with CDH man-

aged in "high-volume" centres.[15, 21] Given the fact that often it is important to have time to look for other anomalies, to discuss potential therapeutic alternatives with the parents, and to engage the opinion of other consultants, our current recommendation is to adopt a conservative approach and delay surgical repair of the CDH until the infant has had an opportunity to stabilize from a hemodynamic and respiratory point of view.[22, 23] Most other studies found associated major anomalies to be important predictors of mortality rate.[24] In our study, all infants affected by other congenital or chromosomal anomaly, non-immune hydrops fetalis or IUGR were deceased.

Judged by descriptions in the literature published during the last decade and data from the International CDH Registry, the use of surfactant has been incorporated as part of a more comprehensive strategy into treatment protocols at many centres worldwide. Therefore, based on the lack of definitive evidence and the availability of only limited studies, administration of surfactant to infants with CDH cannot be recommended, with the exception of participation in well-designed clinical trials, or in the setting of significant prematurity when, besides CDH, the infant may also exhibit respiratory distress due to true surfactant deficiency.[12, 17, 19] A study by Boucherat O *et al.* in human fetuses concluded that CDH does not impair surfactant storage or maturation in the hypoplastic lungs.[22]

The optimal mode of ventilation for patients with CDH is not clear. However, regardless of the ventilatory approach used, management strategies designed to limit lung distension and inspiratory pressures while allowing some degree of permissive hypercapnea are recommended, as they seem to be associated with a higher likelihood of survival.[6, 12, 14, 17, 19]

The effect of INO on the outcome in CDH remains controversial.[20, 25-27] The cardiovascular effects of sildenafil in neonates with CDH and pulmonary hypertension despite optimized ventilatory management, INO and supportive care are not known. Preliminary findings suggest that sildenafil may improve cardiac output by reducing pulmonary hypertension refractory to INO in patients with CDH.[28]

Our and other studies have found birth weight, right side hernia, and pneumothorax to be predictive of mortality in CDH. We also found a significant mortality rate associated to female sex, prenatal diagnosis of CDH, inborn birth, arterial pH<7.35 at admission, the severity of pulmonary hypertension and systemic arterial hypotension. HFOV has also been found to predict mortality when used solely for critically ill infants.[29]

According to the results of a study conducted by the Congenital Diaphragmatic Hernia Study Group, the main determinant of survival in CDH remains the severity of pulmonary hypoplasia and pulmonary hypertension, and the size of diaphragmatic defect correlates well with mortality, as well as morbidity in the live born infants with CDH.[28] In that multicentre study (8 countries, 51 centres, 3062 live born infants) the overall survival was 69%, and the defect size was the most significant factor that affected outcome.[30] In 2001 this same group analysed data submitted on 1054 infants of 71 centers and found the 5 minute Apgar score and bithweight as the most significant predictors of outcome.[31]

Conclusions

Like us, other institutions have improved their survival rate on CDH in the past decade.[32] We observed an improvement in survival rate since 2003, associated to the practice of a new treatment protocol including some of the new therapies. We have tried ECMO in a case of bilateral CDH, without success, and the autopsy revealed severely hypoplastic lungs. We hope ECMO can provide additional advantage, at our NICU, for selected infants in the near future.

Riassunto

Ernia diaframmatica congenita: un'esperienza di 14 anni

Obiettivo. Nel corso degli ultimi due decenni, sono emerse nuove terapie per la gestione dell'er-

nia diaframmatica congenita (CDH). Obiettivo del presente articolo è stato quello di passare in rassegna la nostra esperienza nella gestione di neonati con diagnosi di CDH in un periodo di 14 anni.

Metodi. Review di cartelle cliniche materne e neonatali tra il 1997 e il 2010.

Risultati. Ottanta neonati con diagnosi di CDH, tra cui 21 (26%) pretermine e 28 (35%) con basso peso alla nascita (<2500 g), inclusi 3 (4%) con peso alla nascita estremamente basso (<1500 g). La diagnosi prenatale è stata effettuata in 53 (66%) casi. La sede dell'ernia era: lato sinistro (48 casi, 90,5%), destro (4 casi, 7,5%), bilaterale (1 caso, 1%). La chirurgia correttiva è stata effettuata in 58 pazienti (73%). La ventilazione oscillatoria ad alta frequenza (HFOV) è stata utilizzata in 10 casi (12,5%), il monossido di azoto inalato in 18 casi (22,5%), sildenafil in 15 casi (18,7%) e l'ossigenazione extracorporea a membrana in 1 caso (1%). La sopravvivenza complessiva è stata del 49% (N.=39). Dal 2003, la sopravvivenza complessiva è salita al 64%. Il tasso di sopravvivenza appropriato per i neonati a termine di età gestazionale senza altre anomalie cromosomiche/congenite o idrope fetale era del 67% (24/36).

Conclusioni. Il nostro tasso di sopravvivenza per l'ernia diaframmatica congenita è migliorato negli ultimi 14 anni, associato all'utilizzo di nuove terapie, come la HFOV, il monossido di azoto inalato e sildenafil.

Parole chiave: Ernia congenita diaframmatica - Trattamento - Sopravvivenza, tasso.

References

1. Boloker J, Bateman DA, Wung JT, Stolar CJ. Congenital Diaphragmatic Hernia in 120 infants treated consecutively with permissive hypercapnea/ spontaneous respiration/ elective repair. J Pediatr Surg 2002;37:357-66.
2. Chu SM, Hsieh WS, Lin JN, Yang PH, Fu RH, Kuo CY. Treatment and outcome of congenital diaphragmatic hernia. J Formos Med Ass 2000;99:844-7.
3. Downard CD, Jaksic T, Garza JJ, Dzakovic A, Nemes L, Jennings RW *et al.* Analysis of an improved survival rate for congenital diaphragmatic hernia. J Pediatr Surg 2003;38:729-32.
4. Frenckner B, Ehren H, Granholm T, Linden V, Palmer K. Improved results in patients who have congenital diaphragmatic hernia using preoperative stabilization, extracorporeal membrane oxygenation, and delayed surgery. J Pediatr Surg 1997;32:1185-9.
5. Okuyama H, Kubota A, Oue T, Kuroda S, Ikegami R, Kamiyama M *et al.* Inhaled nitric oxide with early surgery improves the outcome of antenatally diagnosed congenital diaphragmatic hernia. J Pediatr Surg 2002;37:1188-90.
6. Bohn D. Congenital diaphragmatic hernia. Am J Respir Crit Care Med 2002;166:911-5.
7. Cacciari A, Ruggeri G, Mordenti M, Ceccarelli PL, Baccarini E, Pigna A *et al.* High-frequency oscillatory ventilation versus conventional mechanical ventilation in congenital diaphragmatic hernia. Eur J Pediatr Surg 2001;11:3-7.
8. Wilson JM, Lund DP, Lillehei CW, Vacanti JP. Congenital diaphragmatic hernia: a tale of two cities: the Boston experience. J Pediatr Surg 1997;32:401-5.
9. Mallik K, Rodgers BM, McGahren ED. Congenital Diaphragmatic Hernia: experience in a single institution from 1978 through 1994. Ann Thorac Surg 1995;60:1331-5.
10. Kattan J, Godoy L, Zavala A, Faunes M, Becker P, Estay A *et al.* Improvement of survival in infants with congenital diaphragmatic hernia in recent years: effects of ECMO availability and associated factors. Pediatr Surg Int 2010;26:671-6.
11. Azarow K, Messineo A, Pearl R, Filler R, Barker G, Bohn D. Congenital diaphragmatic hernia-a tale of two cities: the Toronto experience. J Pediatr Surg 1997;32:395-400.
12. Doyle NM, Lally KP. The CDH Study Group and advances in the clinical care of the patient with congenital diaphragmatic hernia. Semin Perinatol 2004;28:174-84.
13. Javid PJ, Jaksic T, Skarsgard ED, Lee S, Canadian Neonatal Network. Survival rate in congenital diaphragmatic hernia: the experience of the Canadian Neonatal Network. J Pediatr Surg 2004;39:657-60.
14. Reiss I, Schaible T, van den Hout L, Capolupo I, Allegaert K, van Heijst A *et al.* Standardized postnatal management of infants with congenital diaphragmatic hernia in Europe: The CDH EURO Consortium Consensus. Neonatology 2010;98:354-64.
15. Langham MR, Kays DW, Beierle EA, Chen MK, Mullet TC, Rieger K *et al.* Twenty years of progress in congenital diaphragmatic hernia at the University of Florida. Am Surg 2003;69:45-52.
16. Osiovich HC. Improving survival of neonates with isolated congenital diaphragmatic hernia. Ind Pediatr 2004;41:1138-42.
17. Logan JW, Rice HE, Goldberg RN, Cotton CM. Congenital diaphragmatic hernia:a systematic review and summary of best-evidence practice strategies. J Perinatol 2007;27:535-49.
18. Geggel RL, Murphy JD, Langleben D, Crone RK, Vacanti JP, Reid LM. Congenital diaphragmatic hernia:Arterial structural changes and persistent pulmonary hypertension after surgical repair. J Pediatr 1985;107:457-64.
19. Moya FR, Lally KP. Evidence-Based management of infants with congenital diaphragmatic hernia. Semin Perinatol 2005;29:112-7.
20. Kim DH, Park JD, Kim HS, Shim SY, Kim EK, Kim BI *et al.* Survival rate changes in neonates with congenital diaphragmatic hernia and its contributing favtors. J Korean Med Sci 2007;22:687-92.
21. Javid PJ, Jaksic T, Skarsgard ED, Lee S, Canadian Neonatal Network. Survival rate in congenital diaphragmatic hernia: the experience of the Canadian Neonatal Network. J Pediatr Surg 2004;39:657-60.
22. Boucherat O, Benachi A, Chailley-Heu B, Franco-Montoya ML, Elie C, Martinovic J, Bourbon JR. Surfactant maturation is not delayed in human fetuses with diaphragmatic hernia; 2007.
23. Rozmiarek AJ, Qureshi FG, Cassidy L, Ford HR, Hackman DJ. Factors influencing survival in newborns with congenital diaphragmatic hernia: the relative role of timing of surgery. J Pediatr Surg 2004;39:821-4.
24. Salguero E, Gonzalez de Dios J, Garcia del Rio M, Sanchez Diaz F. Controversies in the therapeutical management of congenital diaphragmatic hernia: update by means of evidence-based medicine. Cir Pediatr 2005;18:170-81.

25. Downard CD, Wilson JM. Current therapy of infants with congenital diaphragmatic hernia. Semin Neonatol 2003;8:215-21.
26. Lally KP. Congenital diaphragmatic hernia. Curr Opin Pediatr 2002;14:486-90.
27. The Neonatal Inhaled Nitric Oxide Study Group (NINOSG). Inhaled nitric oxide and hypoxic respiratory failure in infants with congenital diaphragmatic hernia. Pediatrics 1997;99:838-45.
28. Noori S, Friedlich P, Wong P, Garingo A, Seri I. Cardiovascular effects of sildenafil in neonates and infants with congenital diaphragmatic hernia and pulmonary hypertension. Neonatol 2007;91:92-100.
29. Colvin J, Bower C, Dickinson JE, Sokol J. Outcomes of congenital diaphragmatic hernia:a population-based study in Western Australia. Pediatrics 2005;116:e356-e363.
30. Congenital Diaphragmatic Hernia Study Group. Defect size determines survival in infants with congenital diaphragmatic hernia. Pediatrics 2007;120:e651-e657.
31. Congenital Diaphragmatic Hernia Study Group. Estimating disease severity of congenital diaphragmatic hernia in the first five minutes of life. J Pediatr Surg 2001;36:141-5.
32. van den Hout L, Schaible T, Cohen-Overbeek TE, Hop W, Siemer J, van de Kent K *et al*. Actual outcome in infants with congenital diaphragmatic hernia: the role of a standardized postnatal treatment protocol. Fetal Diagn Ther 2011;29:55-63.

Received on January 27, 2012.
Accepted for publication on November 16, 2012.