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Congenital diaphragmatic hernia and associated omphalocele: a study from the CDHSG registry☆

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ABSTRACT

Background: Congenital Diaphragmatic Hernia (CDH) associated with Omphalocele is a rare condition, and only a few case reports are available in the literature. Both conditions are associated with some degree of pulmonary hypoplasia. We hypothesize that the combination of CDH with Omphalocele might be associated with poorer outcomes.
Aim: The aim of this study was to describe the incidence of this association and postnatal outcomes from the largest database available for CDH.
Methods: Data from the multicenter, multinational database on infants with CDH (CDHSG Registry) born from 2007 to 2018 was analyzed.
Results: A total of 5730 entries were made into the registry during the study period. The incidence of Omphalocele associated with CDH was 0.63% (36 out of 5730).
When comparing posterolateral Bochdalek hernias with Omphalocele (CDH + O) to CDH without Omphalocele (CDH-), CDH + O were born at significantly younger gestational ages. They were sicker directly after birth with significantly lower APGARs at all time points, but received ECMO significantly less often.
The distribution of left vs right side or the defect size did not differ but CDH + O required patch in a significantly larger extent. CDH + O had surgical repair significantly later and had significantly higher rates of non-repairs and significantly lower survival rates. The morbidity was significantly higher with longer hospital stays and higher requirements for O2 at 30 DOL.
Discussion: CDH associated with Omphalocele is a rare but more severe condition with higher mortality and morbidity rates. Newborns with these combined conditions can be difficult to stabilize or might pose complicated management problems due to pulmonary hypertension and/or pulmonary hypoplasia.
Type of Study: Prognosis Study.
Level of Evidence: Level I.

Among patients with congenital diaphragmatic hernia (CDH), associated anomalies have been reported with a frequency of 30–40% [1, 2]. A more recent study identified a frequency of 27% in newborns with CDH [3]. Omphalocele or exomphalos is an associated anomaly characterized by a midline abdominal wall defect with herniated abdominal contents, most commonly liver and intestine, covered by a limiting membrane. Pulmonary hypoplasia and/or pulmonary hypertension are often part of the clinical presentation among patients with Omphalocele [4–6]. The published literature covering CDH with an associated omphalocele is limited to case reports [7, 8] and many of the cases described correspond to anterior/antero-lateral defects [9–12]. Therefore, very little is known about the incidence and outcome of combined omphalocele and posterolateral (Bochdalek) diaphragmatic hernia (CDH). Moreover, infrequent association, along with limited literature, render family counseling challenging with these combined conditions.

The aim of this study was to describe the incidence of this association and the postnatal outcomes using data from the largest database available for CDH.

☆ **Author contributions:** Carmen Mesas Burgos – Study conception, analysis and interpretation of data, drafting of manuscript, critical revision of manuscript
Bjorn Frenckner – analysis and interpretation of data, critical revision of manuscript
Matthew T. Harting – analysis and interpretation of data, critical revision of manuscript
Pamela A. Lally – Acquisition of data, analysis and interpretation of data, critical revision of manuscript
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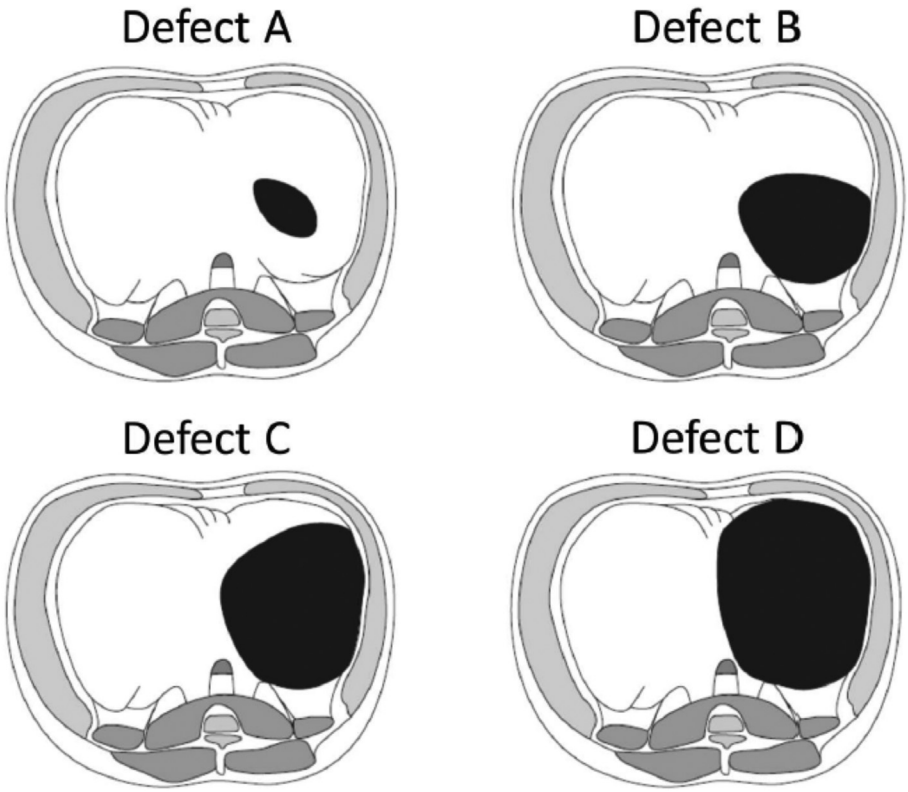

Fig. 1. CDH Study Group Staging System. A left diaphragmatic defect is shown as viewed from the peritoneal cavity looking toward the hemi-thorax. Defects are classified as "A" (smallest, usually "intramuscular" defect with >90% of the hemidiaphragm present; this defect involves <10% of the circumference of the chest wall), "B" (50–75% hemi-diaphragm present; this defect involves <50% of the chest wall), "C" (~25% hemi-diaphragm present; this defect involves >50% of the chest wall), or "D" (largest defect – previously known as "agenesis" with <10% hemi-diaphragm present; this defect involves >90% of the chest wall.

1. Material and methods

The Congenital Diaphragmatic Hernia Study Group (CDHSG) Registry was started in 1995 and collects data on infants with CDH born at or transferred to participating centers. Data about patient demographics, treatment, and outcome until death or discharge (or transfer from) is collected retrospectively from the participating center. [13, 14]. Eighty-three centers contributed data for this study (specified in the Appendix A). [13, 14]. In 2007, the CDH Study Group Staging System for diaphragm defect size was introduced [13, 15] (Fig. 1) and the focus of this study is infants born between January 2007 and December 2018. (See Additional Table.)

Patients with CDH entered in the registry with and without associated Omphalocele were compared with respect to perinatal characteristics, survival rates, defect size and side, associated malformations, use of extra-corporeal membrane oxygenation (ECMO), timing of surgical repair and rates of non-repair, length of hospital stay (LOS) and need for oxygen at 30 days. Patients with ventral/antero-lateral (Morgagni) hernia with and without associated Omphalocele were excluded.

Data are presented as absolute values (n) and percentages (%). Survival to discharge, need for ECMO, survival without ECMO, rates of non-repair and requirement for oxygen at 30 days were analyzed. For categorical data, Fisher's test was performed to investigate differences between groups. For continuous variables, t-test or Mann–Whitney test were used. Kaplan Meier survival analysis was used to illustrate time to event death or time to discharge.

Significance was defined as $p < 0.05$. Analyses were performed using PRISM 8 version 8.0.1 (Graphpad Software Inc., La Jolla, CA) and SPSS® version 24.

The CDHSG registry has been approved for use by the Institutional Review Board of the McGovern Medical School at UT Health in Houston (HSC-MS-03-223).

2. Results

Between 2007 and December 2018, 5730 patients were entered into the registry. 33% of the cases (1896/5730) had at

Additional Table
Single most common associated anomalies.

	n	%
ASD	383	11.4%
VSD	348	10.3%
Dysmorphic features	181	5.4%
CoA	115	3.4%
ASD-VSD	99	2.9%
Skeletal/ribs anomalies	77	2.3%
HLHS	68	2.0%
Hypoplastic aortic arch	63	1.9%
Undescended testis	60	1.8%
Fallot tetralogy	58	1.7%
Hydronephrosis	54	1.6%
BPS	52	1.5%
Hypospadia	40	1.2%
Omphalocele	36	1.1%
Hydrocephalus	36	1.1%
AVSD	34	1.0%
Trisomy18	32	1.0%
Pulmonary stenosis	32	1.0%
Cleft palate	24	0.7%
Trisomy 21	21	0.6%
Hydrops	18	0.5%

Table 1
Associated malformations with CDH 2007–2018.

	n	%
All malformations (in 1896 individuals)	3365	
Cardiac	1604	47.7
Chromosomal	400	11.9
Other	373	9.6
Genito-urinary	323	9.6
GI	204	6.1
Skeletal	152	4.5
CNS-cranial-spine	149	4.4
Lung-airway	111	3.1
Cord anomalies	48	1.4

Table 3
Associated anomalies with CDH + O grouped by organ systems.

CDH + O	n	%
Cardiac	19	44.2
Chromosomal	5	11.6
GI	4	9.3
Genito-Urinary	6	14.0
Skeletal	1	2.3
Other	6	14.0
CNS-cranial-spine	2	4.7

least 1 associated anomaly, with a total of 3365 reported associated anomalies in 1896 individuals. 47.7% of the anomalies were cardiac, and 11.9% of the anomalies were chromosomal anomalies, with many patients having more than one type of anomaly (Table 1).

Thirty-six patients had Omphalocele-Exomphalos representing 1.1% of all reported anomalies (additional material). The rate of Omphalocele associated with Bochdalek hernias was 0.63% (36/5730).

Patients with posterolateral Bochdalek hernias and Omphalocele (CDH + O) were born at significantly younger gestational age than patients with CDH without Omphalocele (CDH-) (38 vs 37 gw, $p = 0.03$), had significantly lower APGARs at birth ($p = 0.001$ at one minute, $p = 0.004$ at 5 minutes), but received ECMO significantly less often (13.9% CDH + O vs 29.1% CDH-,$p = 0.03$) (Table 2).

Forty-two additional malformations were reported, with 19/36 (53%) cases of CDH + O having an additional malformation: 19.4% (7) with one additional malformation, 16.7% (6) with 2 additional malformations and 11.1% (4) had 3 or more additional malformations. The single most common associated additional anomalies were cardiac anomalies (19/42, 44.2%), genitourinary malformations (14.0%), chromosomal anomalies (11.6%), and gastrointestinal atresias (9.3%) (Table 3).

Table 2
Patient's characteristics CDH- and Bochdaleck CDH + O.

Table 2	CDH+ Omphalocele (n = 36)	CDH- (n = 5694)	p Values
	%	**%**	
Bw (median, IQR)	2.5 (2.1–3.0)	3.0 (2.6–3.3)	<0.0001
ECMO	13.9	29.1	0.03
Prenatal Dx	63.9	69.7	ns
APGAR 1 (median, IQR)	3 (1–4)	5 (3–7)	0.004
APGAR 5 (median, IQR)	5 (3–8)	7 (5–8)	0.001
Chromosomal anomalies	13.9	6.6	0.04
Major cardiac anomalies	11.1	8	ns
Other anomalies	27.8	14.1	0.001
Defect size	**n = 18**	**n = 4756**	
A	5.6	13.7	ns
B	33.3	38.9	ns
C	44.4	33.3	ns
D	16.7	14.1	ns
Patch repair	70	44.8	<0.0001
Not repaired	52.8	16.1	<0.0001
DOL at surgery (median, IQR)	7 (4.5–11.5)	5 (3–9)	0.002
Survival	38.8	71.4	<0.0001
DOL at death (median, IQR)	1 (0–13)	11 (1–28)	0.03
LOS (median)*	102 (42–132)	36 (22–68)	<0.0001
Status 30DOL	**n = 16**	**n = 4263**	
Room air	12.5	54	<0.001
O2	87.5	46	<0.001

* *Calculated only for survivors.*

Left vs right side or defect size was similar between CDH and CDH + O but CDH + O required a patch significantly more frequently (70% CDH + O, 44.8% CDH, $p < 0.0001$), had surgical repair significantly later (mean 8.7 days CDH + O, 7.6 mean days CDH, $p = 0.002$), had a significantly higher rate of non-repair (53% CDH + O, % 16% CDH, $p < 0.0001$), and significantly lower survival (39% CDH + O, % 71% CDH, $p < 0.0001$). Those who underwent surgical repair had survival of 82.3% CDH + O (84.6% for CDH-, $p = 0.7$).

Almost 2/3, 63.6%, (14/22) of the deaths in CDH + O patients occurred within the first 48 h of life, compared to 34,6% of CDH- who died within the first 48 h ($p = 0.0064$) (Fig. 2).

CDH + O patients had significantly more morbidity with longer hospital stays and higher O2 requirements at 30 DOL (87.5% CDH + O, 46% CDH, $p < 0.0001$) (Table 4).

3. Discussion

In this study, we report contemporary numbers of associated anomalies with CDH: of the 3365 associated anomalies with CDH patients entered into the registry during the 12 years period, almost half of them are cardiac anomalies. Out of the cardiac anomalies, 46% of them minor anomalies such as ASD and VSD. These rates of associated anomalies with CDH are higher than what it has previously been reported [1, 2] [3].

The incidence of omphalocele in the general population has been reported to be 1/10000 live births [16–19]. The present study shows that omphalocele occurs in ~0.63% of patients with Bochdalek hernias. Given these numbers, a patient with a Bochdalek hernia has an approximately 63x increased risk of having an associated omphalocele (0.63/(1/10000).

CDH associated with major cardiac or chromosomal abnormalities have reportedly worse outcome [20–22]. The results of this study show that the combination of CDH with Omphalocele also results in higher morbidity and mortality, information that can be useful when counseling families.

Pulmonary hypoplasia and pulmonary hypertension are major causes of higher morbidity and mortality in isolated CDH [23–30]. Interestingly, pulmonary hypoplasia [5, 31, 32] and/or pulmonary hypertension [4, 6] have also been found to be associated with isolated omphalocele, and are independent predictors of survival for omphalocele [4, 33, 34].

The underlying pathophysiologic mechanisms behind the various degrees of respiratory insufficiency in infants with omphalocele are poorly understood, but it has been suggested to be related to inadequate lung development as varying degrees of pulmonary hypoplasia have been observed on MRI [31].

Thus, the combination of these two conditions in the developing fetus may lead to a more severe degree of pulmonary hypoplasia and/or pulmonary hypertension, and most likely worsen the degree of respiratory insufficiency experienced after birth, explaining why many of these newborns deteriorate in the immediate post-natal period.

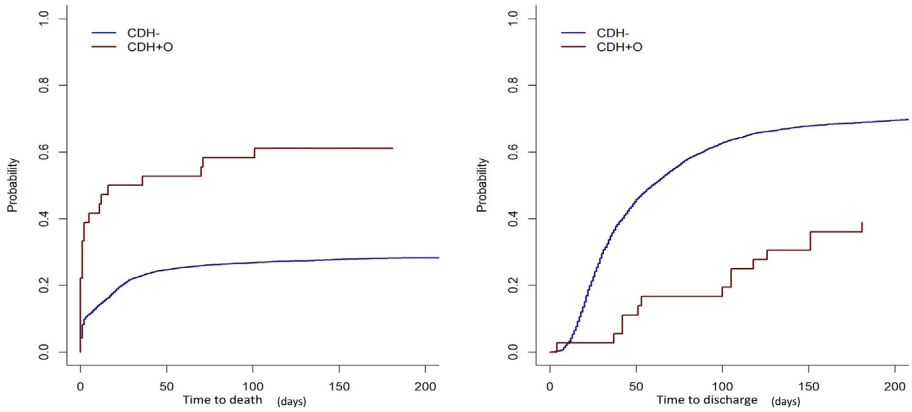

Fig. 2. Kaplan–Meier representing survival curves for CDH- and CDH + O. Time to discharge or to death expressed in days.

Omphalocele is a complex malformation, with frequently associated other anomalies [35–37]. We found a high rate of additional associated anomalies with CDH + Omphalocele (53% of our cohort), which is aligned with recent reports on the contemporary rates of associated anomalies among patients with omphalocele [37]. However, when looking specifically at the rate of associated chromosomal anomalies among our cohort of patients, we found a slightly decreased rate of association, when compared to previous reported rates in isolated omphalocele, 13.9% vs 28%, respectively [37].

Despite a consistently more severe presentation in the perinatal period, newborns with CDH + O received ECLS less frequently than patients with isolated CDH in the study group (1 3.9% vs 29.1%). This may be a selection bias given concerns about the high mortality given the presence of additional associated anomalies, or simply due to a rapid deterioration, profound pulmonary hypertension, and/or pulmonary hypoplasia, rendering them unable to reach even highly aggressive criteria for initiating ECLS.

This is the largest cohort of CDH plus an associated omphalocele, from a multicenter, multinational database focused on CDH. Given the fact that this is a retrospective study, it suffers from the usual limitations. The study group relies on the reporting of member centers, which could alter the true incidence given a limited set of participating centers. Also, the study group represents a collection of centers with a special interest in CDH. Furthermore, the study group only takes into account live-born cases of CDH, missing elective terminations or intra uterine fetal demise, which makes it impossible to calculate the overall incidence of this combined condition. Finally, an additional limitation of this type of study is the fact that the available data are only through discharge, rendering long-term evaluation impossible.

CDH combined with omphalocele is a rare but more severe association with higher rates of mortality and morbidity. Newborns with these combined conditions may be more difficult to stabilize or pose complicated management challenges due to a double-dose of conditions associated with pulmonary hypertension and/or pulmonary hypoplasia.

Table 4
Patient's characteristics of Bochdaleck CDH + O subdivided in patients with/without other anomalies, survivors/not survivors, repair/non repairs.

	CDH + O-other anomalies n = 16	CDH + O + other anomalies n = 20	CDH + O survived n = 14	CDH + O not survived n = 22	CDH + O surgery n = 17	CDH + O non repairs n = 19
%	44.4	56.6	38.8	61.2	47.2	52.8
Bw median (IQR)	2.6 (2.1–3.0)	2.4 (2.0–3.0)	2.9 (2.4–3.2)	2.2(1.9–2.7)	2.8 (2.3–3.1)	2.2 (1.8–3.0)
GA median (IQR)	37.5 (36.2–39.0)	37 (35–39)	38 (37–39)	37 (33–39)	38 (37–39)	37 (33–38)
Prenatal dx (%)	56.3	70	57.1	68.2	70.6	57.9
Male (%)	62.5	55	64.3	54.5	52.9	63.2
Inborn (%)	43.8	65	35.7	68.2	47.1	63.2
Apgar 1 median (IQR)	4 (2–5)	2.5 (1–4)	3.5 (2.7–7)	2 (1–4)	4 (3–7)	2 (1–4)
Apgar 5 median (IQR)	5 (3.7–7.2)	6 (2.2–8)	7.5 (5.7–8.2)	4 (2.2–6)	7 (5.5–8.5)	4 (2–5)
Apgar 10 median (IQR)	6 (5–7)	2.2 (4–7)	6.5 (5.7–7)	6 (4.2–7)	6 (6–7)	6 (4–7)
ECMO (%)	19	10	14.3	13.6	17.6	10.5
Other associated anomalies (%)	0	100	57.1	61.1	64.7	47.4
Defect side Left (%)	81.3	80	78.6	81.8	70.6	89.5
Defect size (n)						
A	1		1		1	
B	4	2	4	2	6	
C	1	7	6	2	8	
D		3	2	1	2	
Patch repair % (n)	66 (4)	81.8 (9)	71.4 (10)	75 (3)	76.5 (13)	0
Not repaired (%)	62.5	45	7 (1)?	81.8	0	100
DOL at surgery median (IQR)	10 (3.5–18.7)	6 (5–9)	8 (5.5–14)	4 (3–6.5)	7 (4.5–11.5)	x
Survival (%)	37.5 (all 6 op survived)	40 (8)	100	0	76.5	5.3 (1)
DOL at death median (IQR)	1 (0.7–6.5)	1 (0–61)		1 (0–13)	70 (44.5–93.5)	1 (0–2.7)
LOS median (IQR)	79 (42–120)	102 (40–151)	102 (42–132)	x	105 (46.5–138.5)	x
O2 at 30 DOL % (n)	83%(5/6)	90% (9/10)	78.6 (11)	100(3)	82.4 (14)	x

Appendix A

Hosp	City	StateProv	Country
Alberta Children's Hospital	Calgary	AB	Canada
Arkansas Children's Hospital	Little Rock	AR	
Astrid Lindgren Children's Hospital	Stockholm		Sweden
Azienda Ospedaliera Papa Giovanni XXIII	Bergamo		Italy
BC Children's & Women's Health Centre	Vancouver	BC	Canada
Cairo University Pediatric Hospital (Aboul Reesh)	Cairo		Egypt
Carolinas Medical Center, Levine Children's Hospital	Charlotte	NC	
Children's Hospital & Research Center Oakland	Oakland	CA	
Children's Hospital at Skanes University Hospital	Lund		Sweden
Children's Hospital Boston	Boston	MA	
Children's Hospital of Akron	Akron	OH	
Children's Hospital of Georgia - AU Health	Augusta	GA	
Children's Hospital of Illinois at OSF St. Francis Med Center	Peoria	IL	
Children's Hospital of Los Angeles	Los Angeles	CA	
Childrens' Hospital of Orange County	Orange	CA	
Children's Hospital of San Antonio	San Antonio	TX	
Children's Hospital of Wisconsin	Milwaukee	WI	
Children's Hospital Omaha	Omaha	NE	
Childrens Hospital, University Bonn	Bonn		Germany
Children's Hospitals and Clinics (Minneapolis)	Minneapolis	MN	
Children's Memorial Hermann Hospital	Houston	TX	
Children's of Alabama	Birmingham	AL	
Cincinnati Children's Hospital Medical Center	Cincinnati	OH	
Cleveland Clinic Foundation – Children's Hospital	Cleveland	OH	
Connecticut Children's Medical Center	Hartford	CT	
Dell Children's Medical Center of Central Texas	Austin	TX	
Duke University Medical Center	Durham	NC	
Emory University	Atlanta	GA	
Golisano Children's Hospital at Strong	Rochester	NY	
Hospital Clinico Universidad Católica de Chile	Santiago	RM	Chile
IRCCS Fondazione Ca′ Granda Ospedale Maggiore Policlinico	Milano		Italy
James Whitcomb Riley Children's Hospital	Indianapolis	IN	
Johns Hopkins All Children's Hospital	St Petersburg	FL	
Johns Hopkins Hospital	Baltimore	MD	
Juan P. Garrahan Children Hospital	Buenos Aires		Argentina
La Paz University Hospital	Madrid		Spain
Le Bonheur Children's Medical Center	Memphis	TN	
Legacy Emanuel Children's Hospital	Portland	OR	
Loma Linda University Children's Hospital	Loma Linda	CA	
Lucile Salter Packard Children's Hospital	Palo Alto	CA	
Mattel Children's Hospital at UCLA	Los Angeles	CA	
Miami Valley Hospital	Dayton	OH	
National Center for Child Health and Development	Tokyo		Japan
NICU Health Sciences Centre	Winnipeg	MB	Canada
Norton Children's Hospital	Louisville	KY	
Osaka University Hospital	Suita-shi	Osaka	Japan
Ospedale Pediatrico Bambino Gesù	Rome		Italy
Palmetto Health Richland	Columbia	SC	
Phoenix Children's Hospital	Phoenix	AZ	
Polish Mother's Memorial Hospital Research Institute	Lodz		Poland
Primary Children's Hospital	Salt Lake City	UT	
Radboud University Nijmegen Medical Centre	Nijmegen		The Netherlands
Rady Children's Hospital	San Diego	CA	
Research Center for Obstetrics, Gynecology and Perinatology	Moscow		Russia
Research Institute at Nationwide Children's Hospital	Columbus	OH	
Royal Children's Hospital	Parkville	Victoria	Australia
Royal Hospital for Sick Children	Glasgow		Scotland
Shands Children's Hospital/University of Florida	Gainesville	FL	
Sophia Children's Hospital	Rotterdam		The Netherlands
St. Francis Children's Hospital	Tulsa	OK	
St. Joseph's Hospital and Medical Center	Phoenix	AZ	
St. Louis Children's Hospital	St. Louis	MO	
St. Louis Univ School of Medicine at SSM Health Cardinal Glennon Children's Hospital	St. Louis	MO	
Stollery Children's Hospital	Edmonton	AB	Canada
Sydney Children's Hospital	Randwick	NSW	Australia
Texas Children's Hospital	Houston	TX	
The Children's Hospital at OU Medical Center	Oklahoma City	OK	
The Children's Hospital of Pittsburgh of UPMC	Pittsburgh	PA	
The Hospital for Sick Children	Toronto	Ontario	Canada

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Appendix A (*continued*)

Hosp	City	StateProv	Country
The Queen Silvia Children's Hospital SU/Östra	Gothenburg		Sweden
Tufts Medical Center	Boston	MA	
UNC School of Medicine	Chapel Hill	NC	
University Childrens Hospital	Uppsala		Sweden
University Malaya Medical Centre	Kuala Lumpur		Malaysia
University of Michigan, C.S. Mott Children's Hospital	Ann Arbor	MI	
University of Nebraska Medical Center	Omaha	NE	
University of Padua	Padua		Italy
University of Texas Medical Branch at Galveston	Galveston	TX	
University of Virginia Medical School	Charlottesville	VA	
Vanderbilt Children's Hospital	Nashville	TN	
Vladivostok State Medical University	Vladivostok		Russia
Winnie Palmer Hospital for Women & Babies	Orlando	FL	
Yale New Haven Children's Hospital	New Haven	CT	

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