Journal of Pediatric Surgery 54 (2019) 2038–2043

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

Early CDH repair on ECMO: Improved survival but no decrease in ECMO duration (A CDH Study Group Investigation)

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ARTICLE INFO

Article history:
Received 9 September 2018
Received in revised form 22 December 2018
Accepted 9 January 2019

Key words:
Congenital diaphragmatic hernia (CDH)
Extracorporeal membrane oxygenation (ECMO)
Thoracic surgery
Abdominal surgery
Neonatal surgery

ABSTRACT

Purpose: "Early on-ECMO" repair of CDH entails repair within 48–72 h of cannulation in an effort to optimize pulmonary physiology, shorten ECMO duration, and, ultimately, improve survival. This study evaluated the effect of early on-ECMO repair as compared to leaving patients unrepaired during ECMO.
Methods: The CDH Study Group database was queried for CDH patients requiring ECMO who either underwent repair within the first 72 h after cannulation or remained unrepaired on ECMO. Primary outcomes were survival to decannulation and ECMO duration.
Results: A total of 248 patients underwent early repair and 922 remained unrepaired on ECMO. The early repair group had increased risk factors for poor outcomes, including higher odds of cardiac defects and thoracic liver location, and lower odds of hernia sac presence. Nonetheless, ECMO survival for the early repair group was 87.1% compared to 78.4% in the unrepaired group ($p = 0.002$). However, the early repair group had a longer median ECMO duration than the unrepaired group (240.6 vs 196.8 h, $p = 0.001$).
Conclusion: While early ECMO repair does not shorten ECMO duration, it results in increased survival to decannulation as compared to those unrepaired on ECMO. This suggests that there may be a physiologic benefit leading to increased ECMO survival in a subset of patients undergoing on-ECMO repair over those designated to undergo post-ECMO repair.
Level of evidence: Level III.

As many as one-third of patients with congenital diaphragmatic hernia (CDH) will require extracorporeal membrane oxygenation (ECMO) [1–3]. Optimal timing of repair of the CDH in patients requiring ECMO remains an area of controversy. Among patients who require ECMO for CDH, there are three general approaches to surgical timing in relation to ECMO cannulation and decannulation. Broadly, these categories are early repair on ECMO (repair within 72 h of cannulation), late repair on ECMO (repair with 72 h of *anticipated* decannulation), and repair following ECMO decannulation ("post-ECMO repair"). The purpose of this study was to determine the impact that early repair on ECMO has on ECMO survival (i.e. survival to ECMO decannulation) and total ECMO duration.

Abbreviations: CDH, Congenital diaphragmatic hernia; ECMO, Extracorporeal membrane oxygenation.

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https://doi.org/10.1016/j.jpedsurg.2019.01.063
0022-3468/

1. Methods

1.1. Study design

The CDH Study Group (CDHSG), which was started in 1995, manages a registry of data relevant to CDH and CDH repair from 114 centers in 15 countries (Appendix 1). Following institutional review board approval, retrospectively-collected patient data were obtained from the CDH SG.

The study was divided into two portions. The first part aimed to determine the influence that early repair of CDH on ECMO has on survival to ECMO decannulation ("ECMO survival") and the second part measured the effect that early repair on ECMO has on ECMO duration.

For both parts of the study, the inclusion criteria were patients with congenital diaphragmatic hernia requiring ECMO prior to CDH repair who either (1) were repaired within 72 h of ECMO cannulation, or (2) were cannulated but never repaired on ECMO. Specifically, this latter group includes both those patients repaired after decannulation (post-ECMO repair) and those who were never repaired.

Exclusion criteria were patients who underwent CDH repair prior to any ECMO cannulation and those with missing data to the degree that they could not be adequately characterized for this study. For the calculation of ECMO duration (the second part of the study), patients who died on ECMO, or on the day of ECMO decannulation, were additionally excluded. The patients who died on the day of decannulation were counted as deaths on ECMO, as many were likely terminal decannulations.

Although patients with multiple ECMO courses were not excluded from this study, only their initial ECMO run parameters were used for analysis.

Data points used for the study were birth weight, estimated gestational age (EGA), in-hospital mortality, day of life (DOL) and time of day at which death occurred, DOL and time of day of ECMO cannulation, DOL and time of day of ECMO decannulation, DOL and time of day of CDH repair, and in-hospital mortality (death during the initial/index hospitalization following birth).

Additionally, the following "severity factors" were also collected: side of CDH, repair type (patch or primary repair), presence of hernia sac, liver location (abdomen or chest), presence of congenital cardiac abnormality, and severity of congenital cardiac abnormality (major or minor). Isolated patent foramen ovale or patent ductus arteriosus was classified as "minor" congenital cardiac anomalies, and all other congenital cardiac anomalies (or combinations thereof) were considered "major".

1.2. Statistical methods

Examination of data included descriptive statistics and assessment of distributional shape for discrete and continuous variables with frequencies and percentages calculated for categorical variables.

Analysis focused on the potential differences and relationships between the variables detailed above in relation to the comparator groups described. Potential differences were assessed utilizing the Student's t-Test and Wilcoxon Rank Sum test for normally and nonnormally distributed discrete and continuous data. Potential relationships were examined utilizing the χ^2 test of independence where indicated. Unless otherwise noted, all testing was two-tailed and evaluated at the type I error rate of $\alpha = 0.05$ level of statistical significance.

Table 1
Baseline characteristics for patients repaired early on ECMO and those not repaired on ECMO.

	Mean	SD	Median	LQ	UQ	Min	Max
Early repair on ECMO (n = 248)							
Birth weight (kg)	3.1	0.5	3	2.7	3.4	1.5	4.6
EGA (weeks)	37.8	1.8	38	37	39	32	42
Not repaired on ECMO (n = 922)							
Birth weight (kg)	3.1	0.5	3.1	2.7	3.4	1.4	5.1
EGA (weeks)	38.1	1.7	38	37	39	30	42

Abbreviations: EGA, estimated gestational age; SD, standard deviation; LQ, lower quartile; UQ, upper quartile.

As the exclusion criteria were different for the calculation of ECMO survival and duration, the abovementioned "severity factors" (see Section 2.1) were compared separately for these two endpoints.

Local data storage and manipulation were performed in Excel 16.10 (Microsoft Corporation, Redmond, Washington, USA) and statistical analyses were completed using SAS 9.4 / 13.2 (SAS Institute, Cary, North Carolina, USA).

2. Results

2.1. ECMO survival

There were a total of 2428 patients with CDH who required ECMO. After applying the aforementioned inclusion and exclusion criteria, there were 1170 patients analyzed for this study. A total of 248 patients underwent early repair and 922 were not repaired on ECMO (Fig. 1). In the former group, 21 required repeat ECMO runs (8.5%) and in the latter group, 48 required repeat ECMO runs (5.2%).

Those repaired early on ECMO had an 87.1% rate of survival to ECMO decannulation ("ECMO survival") while those not repaired on ECMO had only 78.4% ECMO survival.

There was no significant difference in the two groups in terms of birth weight or EGA (*p-values* 0.79 and 0.051, respectively). See Table 1 for additional details.

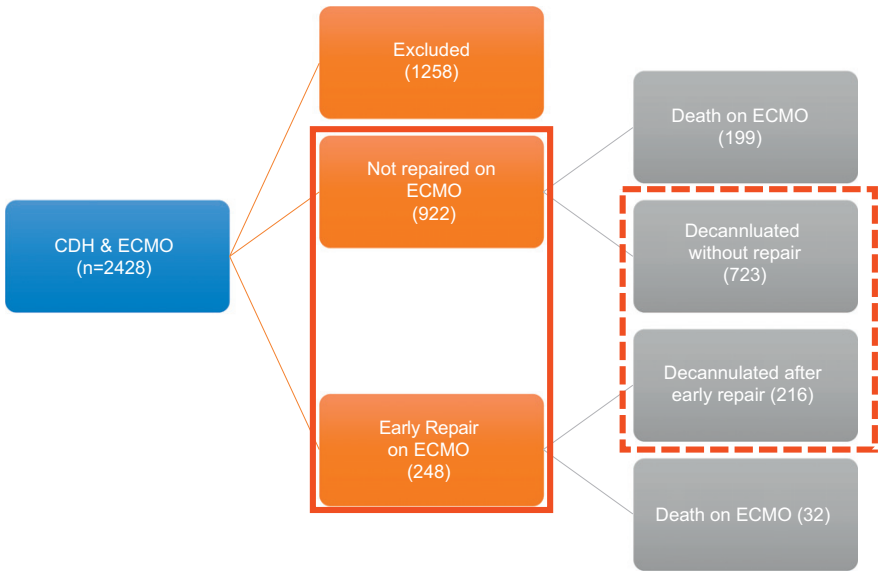

Fig. 1. Flowchart demonstrating patient allocation. The solid line depicts those patients used for the portion of the study involving survival to ECMO decannulation. The broken line indicates those patients used for the portion of the study examining ECMO duration.

Table 2
Comparison of severity factors between patients repaired early on ECMO and those not repaired on ECMO.

	Early repair (n = 248)	No repair on ECMO (n = 922)	*p-value*	OR	95% CI	
ECMO Survival (%)	216 (87.1%)	723 (78.4%)	0.002	1.85	1.23	2.78
Survival to discharge (%)	145 (58.4%)	445 (48.3%)	0.004	1.52	1.14	2.00
Patch repair (%)	211 (85.0%)	439 (75.8%)	0.002	1.85	1.23	2.78
Hernia sac presence (%)	13 (5.2%)	63 (10.9%)	0.009	0.45	0.24	0.83
Liver down (%)	27 (10.9%)	107 (11.6%)	0.001	0.46	0.29	0.75
Presence of CHD (%)	58 (23.4%)	159 (17.2%)	0.031	1.45	1.03	2.04
Major CHD (%)	25 (10.1%)	65 (7.0%)	0.769			
Left side CDH (%)	189 (76.2%)	724 (78.5%)	0.310			

For relationships which were statistically significant, as determined by the chi-squared test, odds ratios (ORs) were calculated. The OR is presented for the early repair group relative to the group not repaired on ECMO. For example, the odds of survival to ECMO decannulation are 1.85 times higher for those in the early repair group. Values for patch repair and hernia sac presence were only calculated for those patients who underwent surgical repair. Abbreviations: CI, confidence interval; CHD, congenital heart disease.

An odds ratio (OR) was calculated for those relationships which were demonstrated to be significant by the χ^2 test (Table 2). In brief, the early repair group had higher odds of ECMO survival, survival to hospital discharge, use of a patch for CDH repair, and the presence of a congenital cardiac anomaly. Conversely, the early repair group had lower odds of hernia sac presence and abdominal liver location (liver down).

Of note, while the purpose of this segment of the study was not to examine ECMO length, post-hoc analysis, including those who died on ECMO, showed that the group not repaired on ECMO had a shorter ECMO duration than the early repair group (median 196.1 h versus 245.3 h, *p-value* < 0.001).

2.2. ECMO duration

For the determination of ECMO duration (where those who died on ECMO or the day of ECMO decannulation were excluded), there were 939 patients, with 216 undergoing early repair and 723 patients decannulated without repair on ECMO (Fig. 1).

The group surviving to decannulation without repair had a shorter duration of ECMO (median 196.8 h, mean 227.3 h) than the group repaired early on ECMO (median 240.6 h, mean 270.2 h), and this difference was statistically significant (*p-value* = 0.001). See Table 3 for full details.

For this portion of the study, all testing was two-tailed and evaluated at the Bonferonni adjusted type I error rate of $\alpha = 0.025$ level of statistical significance.

There was no significant difference in the two groups in terms of birth weight or EGA (*p-values* 0.57 and 0.083, respectively). See Table 4 for additional details.

An odds ratio (OR) was calculated for those relationships which were demonstrated to be significant by the χ^2 test (Table 5). In short, the early repair group, once again, had higher odds of use of a patch for CDH repair and the presence of a congenital cardiac anomaly. Conversely, the early repair group had lower odds of hernia sac presence and abdominal liver location.

3. Discussion

This study sought to determine the effect of early repair of CDH on ECMO (within 72 h of cannulation). Due to the size of the CDHSG database, this study represents one of the largest studies of timing of CDH repair for patients requiring ECMO. The results demonstrate that patients repaired early on ECMO have higher rates of ECMO survival to decannulation and survival to hospital discharge when compared to patients not repaired on ECMO. Notably, the early ECMO group had improved ECMO and hospital survival despite also having higher rates of features associated with worse outcomes in patients with CDH including absence of hernia sac [4–6], thoracic liver location [7–9], presence of congenital heart disease [10], and the need for prosthetic patch for CDH repair [11,12]. Nevertheless, the early repair group had a longer median duration of ECMO.

3.1. Study design

There were multiple considerations regarding study design which warrant discussion.

The study compared patients repaired early on ECMO to those not repaired on ECMO, who were presumably planned to undergo repair postdecannulation. This comparison was felt to be "cleaner" and less prone to bias, as 0–3 days following ECMO cannulation is likely too early for the treatment team to presume their prognosis and thereby introduce significant bias. Additionally, while repair just prior to decannulation can be the result of a clinician deciding based on the patient's real time prognosis, those left to be decannulated without repair can be considered a group with less prognostic bias as those patients are made up of those left unrepaired, both improving and declining, by clinicians who likely don't believe CDH repair will assist in stabilizing the patient's physiology. Furthermore, examination of patients not repaired on ECMO helps to establish a baseline, demonstrating how patients fare on ECMO in the absence of repair.

It may be curious to some that the group of patients not repaired on ECMO includes patients who were never repaired. The group was designed this way because in a real clinical scenario, patients not undergoing early repair who are intended for repair following decannulation will not always survive to repair. This can be viewed akin to an "intention to treat" (ITT) analysis. Patients not repaired on ECMO can be considered to be in

Table 3
ECMO duration statistics, given in hours, for patients repaired early on ECMO (excluding deaths on ECMO) and those decannulated from ECMO without repair.

	Mean	SD	Median	LQ	UQ	Min	Max
Early repair on ECMO (n = 216)	270.2	152.1	240.6	148.3	353.7	65.7	910.9
Decannulated without repair (n = 723)	227.3	125.1	196.8	139.5	295.1	4.5	1060

Abbreviations: SD, standard deviation; LQ, lower quartile; UQ, upper quartile.

Table 4
Baseline characteristics for patients repaired early on ECMO (excluding deaths on ECMO) and those decannulated from ECMO without repair.

	Mean	SD	Median	LQ	UQ	Min	Max
Early repair on ECMO (n = 216)							
Birth weight (kg)	3.1	0.5	3	2.7	3.5	1.6	4.6
EGA (weeks)	37.9	1.8	38	37	39	32	42
Decannulated without repair (n = 723)							
Birth weight (kg)	3.1	0.5	3.1	2.8	3.4	1.6	5.1
EGA (weeks)	38.2	1.6	38	37	39	32	42

Abbreviations: EGA, estimated gestational age; SD, standard deviation; LQ, lower quartile; UQ, upper quartile.

Table 5
Comparison of severity factors for patients repaired early on ECMO and those decannulated from ECMO without repair.

	Early repair (n = 216)	Decannulated without repair (n = 723)	*p-value*	OR	95% CI	
Survival to discharge (%)	145 (67.1%)	445 (61.5%)	0.136			
Patch repair (%)	182 (84.3%)	436 (75.7%)	0.011	1.69	1.12	2.56
Hernia sac presence (%)	10 (4.6%)	63 (10.9%)	0.006	0.39	0.19	0.77
Liver down (%)	26 (12.0%)	107 (14.8%)	0.011	0.53	0.32	0.86
Presence of CHD (%)	53 (24.5%)	116 (16.0%)	0.005	1.69	1.17	2.45
Major CHD (%)	21 (9.7%)	49 (6.8%)	0.749			
Left side CDH (%)	164 (75.9%)	568 (78.6%)	0.402			

For relationships which were statistically significant, as determined by the chi-squared test, odds ratios (ORs) were calculated. The OR is presented for the early repair group relative to the group decannulated from ECMO without repair. Values for patch repair and hernia sac presence were only calculated for those patients who underwent surgical repair. Abbreviations: CI, confidence interval; CHD, congenital heart disease.

the repair after ECMO decannulation ("post-ECMO repair") ITT group. Whether or not these patients received repair or died before they could have surgery, they were included in the post-ECMO repair group as in the clinical realm, survival to decannulation can be seen as a legitimate and reasonable short term goal in and of itself.

A "post-ECMO CDH repair group" was not specifically used in this study because, by definition, the group of patients repaired following ECMO decannulation would have a 0% on-ECMO mortality rate for their first ECMO course. Therefore, it would be inappropriate to compare early repair patients to post-ECMO repair patients, as the latter group has already eliminated patients who were not able to be decannulated. In other terms, the post-ECMO group may be selecting for a healthier population who was able to wean from ECMO.

One of the advantages of studying the early repair group is that the study population is very easy to identify. In contrast, patients repaired later in their course of ECMO may be undergoing late repair on ECMO because they have exhibited physiologic improvement and demonstrated their stability for decannulation. On the other hand, they may be undergoing repair as a "Hail Mary" attempt in a patient who has failed to demonstrate clinical improvement. For this reason, late repair patients were specifically not examined by this study. Similarly, comparing early repair patients to all patients not repaired on ECMO (as opposed to just those who were repair following decannulation) removes the guesswork in attempting to determine which patients were truly post-ECMO repairs "by design."

In formulating the exclusion criteria, on-ECMO mortality was excluded for the calculation of ECMO duration due to concern that including on-ECMO mortalities could artificially increase or decrease the ECMO duration for both groups. Post-hoc analysis (Section 3.1) demonstrated that not only was there only a minimal difference in ECMO duration for each group with application of the exclusion criteria, but the early repair group still had a longer duration of ECMO when not excluding those patients who died on ECMO.

Death on the day of ECMO decannulation was counted toward on-ECMO deaths to account for patients who died immediately following decannulation, such as those patients who were "terminally decannulated."

3.2. Perspective

One of the significant advantages of using the CDH SG database is the large number of patients contained within the database. While CDH is a heavily-studied area of pediatric surgery, it is a rare enough disease that investigations from single institutions generally suffer from small sample sizes. This study represents one of the largest studies to date examining timing of CDH repair in patients requiring ECMO. However, one of the disadvantages of the database is the lack of homogeneity. There are undoubtedly significant variations between institutions in perinatal and perioperative management of these CDH patients. Furthermore, the practices of institutions who contribute more heavily to the database may potentially bias the database findings. Finally, there may also be variability introduced by the fact that data were collected longitudinally over a number of years. The passage of time was likely accompanied by alterations in practice and management.

One oft-cited reason for avoiding any type of repair on ECMO is hemorrhagic complications. However, it has been demonstrated that bleeding risk may be mitigated by antifibrinolytics, such as aminocaproic acid and tranexamic acid [13]. In one study, early repair and post-ECMO repair were not shown to have a significant difference in major bleeding complications [14].

Another possible misconception associated with ECMO repairs is that (early) ECMO repair may help to decrease the total ECMO duration. However, this study demonstrated that patients repaired early on ECMO actually had a longer duration of ECMO than those not repaired on ECMO. Other, smaller studies have demonstrated similar findings.

A study conducted by Partridge et al showed that the 41 patients with CDH repaired on ECMO (without specific analysis of the early repair group), demonstrated a median ECMO duration of 452 h with 44% survival to discharge [15]. The survival rate from that study is comparable to both groups in the present study. While the Partridge study shows a substantially longer ECMO duration than the present study, it showed that the group repaired on ECMO (again, not specifically looking at those repaired early) had a longer duration of ECMO than those repaired post-ECMO.

Fallon et al performed a study of 46 patients, comparing outcomes for different repair timing relative to ECMO [14]. Much like the current study, patients repaired early on ECMO had a longer ECMO duration compared with those repaired post-ECMO (12 vs 10 days). However, this difference was not statistically significant. Of note, the early repair group had a significantly shorter ECMO duration than the late ECMO repair group (18 days). The comparison between ECMO duration for the early and post-ECMO repair groups may be experiencing a type II error due to the small number of patients involved in the study. Furthermore, the comparison between early and late ECMO repairs may be biased by the fact that the late ECMO repair group must have a *minimum* of 72 h on ECMO to be included in the late group.

Dassinger et al specifically analyzed patients repaired within 72 h of ECMO cannulation [16]. The findings were a median duration of ECMO of 11.7 days and a mean of 10 days, with survival of 71%. Unfortunately, the paper does not explain how survival was defined. Assuming this is survival to hospital discharge (as was used in this CDHSG study), then the Dassinger paper has a significantly higher hospital survival rate, but comparable ECMO length. As this study was performed at only one institution, this difference in mortality may suggest different criteria for offering patients ECMO or perhaps demonstrates the benefits of standardizing therapy.

The aforementioned studies have findings which are consistent with our presented data. However, this study has the added benefit of using an intention-to-treat comparison for patients not repaired early on ECMO. This may help to provide guidance to surgeons when determining if a patient should be directed toward early or post-ECMO repair.

3.3. Limitations, uncertainties, and future directions

As with any study conducted using the CDHSG database, the intentions of the surgeons are unknown. Thus, one could argue that while patients repaired in the early group did not have a chance to physiologically declare themselves, patients anticipated to have very severe disease (such as an unfavorable lung-to-head ratio or observed-to-expected total fetal lung volume ratio) could have been chosen to not be included for the early repair group. However, this argument is partially invalid, as evidenced by the fact that when studying on-ECMO mortality between those repaired on ECMO and those not repaired on ECMO, the early repair group was noted to be an overall higher risk group.

In addition to surgeon preference and intention, the norms and policies of the institutions treating patients are unknown. The CDHSG database unfortunately does not identify which institution treated a patient. Furthermore, it is unknown which centers, if any, preferentially offer one treatment approach (such as early repair on ECMO) over another. This has the potential to introduce a bias which would be impossible to detect or eliminate.

It may be concluded that the higher rate of survival to ECMO decannulation in the early repair group was due to improvement of the patient's physiologic parameters. However, if that were the case, one would expect the early repair group to also have a shorter duration of ECMO. The results of this study did not demonstrate that to be true. This may be due to the heterogeneity of the patients in the early repair group. We conjecture that there is a certain subset of severe CDH patients who benefit from early repair on ECMO. In the present study, it may have been early repair of this group which led to the higher overall ECMO survival rate for patients repaired early on ECMO. However, the majority of patients with CDH requiring ECMO may not benefit from early repair on ECMO, or may even have *increased* ECMO duration as a result. This may account for the early repair group having a longer ECMO duration in our study.

The authors agree that the thought of repairing all CDH patients requiring ECMO while they are on ECMO is daunting, and this is not being advocated at present. Further investigations should include an examination of patient outcomes while controlling for patient severity factors, as well as providing details of any bleeding complications. Additionally, more specific preoperative factors need to be identified to predict which patients benefit the most from early repair or post-ECMO repair.

4. Conclusion

The results of this study demonstrate that early repair on ECMO is associated with a higher ECMO survival rate and higher survival to hospital discharge rate, when compared with patients not repaired on ECMO. However, patients repaired early on ECMO experience a longer ECMO duration.

Funding sources

None.

Declaration of interest

The authors have no relevant disclosures or conflicts of interest.

Acknowledgments

Special thanks to our biostatistician, Neil L. McNinch, MS, RN of the Akron Children's Hospital Rebecca D. Considine Research Institute (Akron, OH), for his contributions to the statistical analysis.

Appendix 1. The list of institutions that contributed to the Congenital Diaphragmatic Hernia Study Group database

Hosp	City	State/Prov	Country
Advocate Lutheran General Hospital	Park Ridge	IL	
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
Carolinas Medical Center, Levine Children's Hospital	Charlotte	NC	
Cedars Sinai Medical Center	Los Angeles	CA	
Central Hospital Aichi Prefectural Colony	Kasugai	Aichi	Japan
Children's Hospital & Research Center Oakland	Oakland	CA	
Childrens Hospital at Skanes University Hospital	Lund		Sweden
Children's Hospital Boston	Boston	MA	
Children's Hospital of Akron	Akron	OH	
Children's Hospital of Buffalo	Buffalo	NY	
Children's Hospital of Illinois	Peoria	IL	
Children's Hospital of Los Angeles	Los Angeles	CA	
Children's Hospital of Michigan	Detroit	MI	
Children's Hospital of Oklahoma	Oklahoma City	OK	
Children's Hospital of Philadelphia	Philadelphia	PA	
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 Mercy Hospitals & Clinics	Overland Park	KS	
Children's National Medical Center	Washington	DC	
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	
Cook Children's Medical Center	Ft. Worth	TX	
Dell Children's Medical Center of Central Texas	Austin	TX	
Duke University Medical Center	Durham	NC	
Emory University	Atlanta	GA	
Freie Universitat Berlin	Berlin		Germany
Georgia Health Sciences University	Augusta	GA	
Golisano Children's Hospital at Strong	Rochester	NY	
Hasbro Children's Hospital, Brown Medical School	Providence	RI	
Helen DeVos Children's Hospital	Grand Rapids	MI	
Hershey Medical Center	Hershey	PA	
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	
Juan P. Garrahan Children Hospital	Buenos Aires		Argentina
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	
Massachusetts General Hospital	Boston	MA	
Mattel Children's Hospital at UCLA	Los Angeles	CA	
Mayo Clinic	Rochester	MN	

(continued)

Hosp	City	State/Prov	Country
Medical College of Virginia	Richmond	VA	
Medical University of South Carolina	Charleston	SC	
Miami Valley Hospital	Dayton	OH	
National Center for Child Health and Development	Setagaya-ku	Tokyo	Japan
NICU Health Sciences Centre	Winnipeg	MB	Canada
North Carolina Baptist Hospital	Winston-Salem	NC	
Norton Children's Hospital	Louisville	KY	
Oespedale Pediatrico Bambino Gesu	Rome		Italy
Osaka Medical Center for Maternal and Child Health	Izumi	Osaka	Japan
Osaka University Graduate School of Medicine	Suita	Osaka	Japan
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
Rainbow Babies and Children Hospital	Cleveland	OH	
Research Center for Obstetrics, Gynecology and Perinatology	Moscow		Russia
Research Institute at Nationwide Children's Hospital	Columbus	OH	
Rockford Memorial Children's Hospital	Rockford	IL	
Royal Alexandra Hospital	Edmonton	Alberta	Canada
Royal Children's Hospital	Parkville	Victoria	Australia
Royal Hospital for Sick Children	Glasgow		Scotland
Salesi Children's Hospital	Ancona		Italy
San Diego Children's Hospital	San Diego	CA	
Santa Rosa Children's Hospital	San Antonio	TX	
Shands Children's Hospital/University of Florida	Gainesville	FL	
Sophia Children's Hospital	Rotterdam		The Netherlands
St. Christopher's Children's Hospital	Philadelphia	PA	
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	
St. Paul Campus Children's Minneapolis	Minneapolis	MN	
Stollery Children's Hospital	Edmonton	Alberta	Canada
Sydney Children's Hospital	Randwick	NSW	Australia
T.C. Thompson Hospital	Chattanooga	TN	
Texas Children's Hospital	Houston	TX	
The Children's Hospital of Pittsburgh of UPMC	Pittsburgh	PA	
The Hospital for Sick Children	Toronto	Ontario	Canada
Tufts Medical Center	Boston	MA	
Tulane University Hospital	New Orleans	LA	
UNC School of Medicine	Chapel Hill	NC	
Universitatsklinikum Mannheim gGmbH	Mannheim		Germany
University Hospital Gasthuisberg	B-3000 Leuven		Belgium
University Malaya Medical Centre	Kuala Lumpur		Malaysia
University of California San Diego	San Diego	CA	
University of Chicago	Chicago	IL	
University of Kentucky Medical Center	Lexington	KY	
University of Michigan, C.S. Mott Children's Hospital	Ann Arbor	MI	
University of Mississippi Medical Center	Jackson	MS	
University of Nebraska Medical Center	Omaha	NE	

(continued)

Hosp	City	State/Prov	Country
University of New Mexico Children's Hospital	Albuquerque	NM	
University of North Carolina	Chapel Hill	NC	
University of Padua	Padua		Italy
University of Puerto Rico Medical Center	San Juan	Puerto Rico	
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
Wilford Hall USAF Medical Center	Lackland AFB	TX	
Winnie Palmer Hospital for Women & Babies	Orlando	FL	
Yale New Haven Children's Hospital	New Haven	CT	

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