ARTICLE

Medical Interventions and Survival by Gender of Children With Trisomy 18

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Research has typically shown limited aggressive medical interventions and low survival rates for children with full trisomy 18. Recent studies provide more positive results. This study examined 82 children with full trisomy 18 drawn from the Tracking Rare Incidence Syndromes (TRIS) project database. Children were classified into three groups according to the highest intervention received: "hospice or no intervention" (n = 5, 6.1%), "necessary interventions (enteral feeding, ventilator use)" (n = 46, 56.1%), and "aggressive interventions (surgery)" (n = 31, 37.8%). Seven of 14 male children (50%) and 52 of 68 female children (76.5%) were living at the time of survey completion. Additionally, information about any interventions used during the care of these children was also provided. It was found that three males (37.5%) and 28 females (48.3%) had used hospice care at some point; 12 males (85.7%) and 61 females (89.7%) received enteral feeding at some point; 7 males (58.3%) and 25 females (38.5%) had ventilator; and 7 males (50%) and 33 females (48.5%) underwent some form of surgery. These results suggest improved outcomes when given necessary and aggressive medical interventions. Implications and recommendations for further research are provided.

KEY WORDS: trisomy 18; medical interventions; long-term survival; gender

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INTRODUCTION

As initially described by Edwards in 1960, trisomy 18, also known as Edwards syndrome, is the second most common autosomal trisomy syndrome after trisomy 21 (Down syndrome) [Rasmussen et al., 2003; Lakovschek et al., 2011]. Trisomy 18 occurs as a result of the presence of a third chromosome 18 during meiosis, primarily due to nondisjunction. Full trisomy 18 is most common. In this case, the extra chromosome occurs in all body cells.

Survival rate for full trisomy 18 (t18) is approximately 10% for children that live past their first birthday [Cereda and Carey, 2012]. Additionally, life expectancy has been shown to be longer for females with full t18 than for males [Hsaio et al., 2009; Rosa et al., 2011; Wu et al., 2013]. As such, this disorder has been described as lethal due to the reported low survival rate [Bos and Broers, 1992; Goc et al., 2006; McGraw and Perlman, 2008; Li and Liu, 2012; Pruszewicz et al., 2014]. Hospice care is frequently recommended to keep the child comfortable and pain-free. Parents are often told that t18 is "incompatible with life" and, thus, medical interventions are not justified [Hentschel et al., 2006; Breeze et al., 2007; Romesberg, 2007; Everett and Albersheim, 2011; Li and Liu, 2012; Merritt et al., 2012; Pruszewicz et al., 2014].

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disorder has been described as lethal due to the reported low survival rate.

Yet, as increasingly noted in current research, the use of medical interventions for children with t18 may increase their long-term survival [Kosho et al., 2006; Kaneko et al., 2008; Kosho, 2008; Kobayashi et al., 2010; Maeda et al., 2011; Kosho et al., 2013; Bruns and Campbell, 2014; Nelson et al., 2016]. Medical interventions can include the use of no interventions, which is considered hospice care, necessary medical interventions to include feeding assistance and artificial ventilation, and aggressive medical interventions to include cardiac/major organ surgery and/or respiratory assistance. For example, in a Japanese study, children offered cardiac surgery demonstrated longer survival than those not given aggressive medical interventions [Kosho et al., 2013]. Medical interventions for children with t18 may also promote better quality of life and facilitate their reaching key developmental milestones. An example of such a milestone is the use of gestures and vocalizations to communicate [Watkins, 2011; Bruns, 2015]. These positive results challenge the belief that aggressive medical interventions do not affect mortality of children with t18. It is possible that these findings suggest a possible paradigm shift from non-intervention to intervention [Hsiao et al., 2009; Showalter, 2009; Yates et al., 2011; Bruns and Campbell, 2014; Lorenz and Hardart, 2014; Nelson et al., 2016].

Support groups and social media often portray a more positive outlook as well as emphasize long-term survivors. According to Janvier et al. [2012], parents expressed concerns that interventions were not being offered due to their child's diagnosis. For instance, out of 332 questionnaires completed by parents, 87% (n = 288) stated that their physicians told them that this condition was incompatible with life. Furthermore, 50% of parents stated that their physicians told them that their child would be in a vegetative state, and 37% of parents felt judged for asking for care for their child with t18.

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An additional example is from the American Academy of Pediatrics Resuscitation Program with a recommendation, "...against newborn resuscitation for lethal chromosomal anomalies" [cited in Guon et al., 2014, p. 309]. Yet, in a mixed-methods study, the majority of parents (n = 209, 63%) felt that some providers did not look at their child individually but rather as a disorder [Guon et al., 2014]. Of the 107 children involved in this study, 25% received aggressive medical interventions, and 53% received hospice care (also referred to as comfort care)/interventions. Guon et al. also noted,

Children who received comfort care were more likely to die in their first day of life compared to children who received interventions. Children who received interventions were also more likely to live longer than 1 year than children who received comfort care (p. 213).

The purpose of this study was to investigate to what extent, survival in months, differed as a function of medical interventions (hospice care/interventions, necessary medical interventions, aggressive medical interventions) and gender in a sample of children with t18 drawn from the Tracking Rare Incidence Syndromes (TRIS) project database.

METHODS

The data presented here was obtained from the TRIS project. At present, the project includes a database of approximately 1,000 children. This study focused on data collected from parents/guardians with a child with t18.

Instrumentation

The TRIS project includes several surveys for data collection. The focus here is the survey developed for children living 2 months or longer (TRIS Survey). The survey was developed from the following sources: (i) medical literature from 1990 to 2005; (ii) rare trisomy specific parent listservs; and (iii) printed materials from the Support Organization for Trisomy 18, 13, and related disorders (SOFT). The TRIS Advisory Committee provided initial input to development of the TRIS database. This group was comprised of parents of living and deceased children with rare trisomy disorders, medical professionals, and educational personnel with specialized knowledge.

The TRIS Survey consists of three parts. Part I consisted of 35 items regarding pregnancy and birth history along with demographics. Part II included 60 items regarding medical health concerns. Part III is comprised of 46 items regarding social supports and resource needs. Demographic information is also collected including child's age at time of survey completion, and parent marital status and educational level. The first publication of TRIS project data was in 2008 [Bruns, 2008].

Procedure

In January 2007, the TRIS project received approval from the Southern Illinois University's Human Subjects Committee to begin data collection. Informed consent is collected from participants prior to survey access. A cover letter outlines confidentiality and anonymity.

Recruitment procedures included parent-to-parent contact, listservs,

Facebook, SOFT conferences, articles in the SOFT newsletter, blog posts through the Global Genes Project, and the TRIS project brochure. Participants submit their and their child's name, date of birth (and death, if appropriate) and trisomy type, geographic location, and email address through a link on the TRIS project website. A unique login and password to access the survey is emailed to the participant within 48 hr and used for the duration of project participation.

Selection criteria was based on diagnosis of full trisomy 18 and completed responses to TRIS Survey items focusing on hospice care, necessary medical interventions including feeding, and respiratory assistance as well as aggressive medical interventions including cardiac or major organ surgeries.

Data Analysis

This study was completed using statistical analysis of archival data from the TRIS project survey with parent/guardian-provided information about children with t18. Parent-reported data from the TRIS project was data mined containing quantitative data that provided a larger total sample size than used in previous studies, taking into account the uniqueness of this population.

Inferential statistics (e.g., factorial analysis of variance [ANOVA]) were performed. However, the assumptions of the factorial ANOVA were violated. Specifically, the distributions of age overall, and the component gender as well as highest level of intervention categories were not approximately normally distributed. Some categories also did not exhibit homogeneity of variance. As such, the descriptive statistics yielded relevant results that will be further explained.

Analysis was calculated on pairs of variables used to observe the descriptive relationship between types of medical interventions, survival age and gender. This will address necessary medical interventions such as enteral feeding and the use of a ventilator along with aggressive medical interventions such as surgery.

Participants

The sample described here was drawn from the TRIS project database. At the time of the start of data mining, 334 surveys were completed with 83 children with a diagnosis of t18 (24.9%). Data are available for 82 children (24.3%) due to one participant not completing all necessary survey items. In addition, children with mosaic or partial forms of t18 were excluded.

There were more females (n = 68, 82.9%) than males (n = 14, 17.1%) in the sample. In addition, over 70% of children were living at time of survey completion (n = 59). Mean age of this group was 70 months. Median age of this group was 48 months. It is important to note that the median age was less than the mean age due to a skewed distribution.

Based on responses from 82 participants (98.8%), 70 parents were married (85.4%) and 31 completed 13–16 years of formal schooling (37.3%). In contrast, two participants reported 0–9 years of education (2.4%). Most participants selected medium income level (n = 65, 79.3%). (Dollar amounts were not assigned to income levels due to the international scope of the project.) Table I provides additional demographic information.

RESULTS

Overall, most children with t18 received either necessary interventions such as enteral feeding (n = 73, 89.0%) and/or aggressive interventions such as surgical procedures (n = 40, 48.8%).

Level of Intervention

The data described below represents 14 males (17.1%) and 68 females (82.9%) for a total sample of 82 children represented in this study. There were 59 children living at the time of survey completion (72.0%) with 7 males (50.0%) and 52 females (76.5%). Results provide information on the range of interventions received across the sample as well as survival and gender differences.

No interventions

There were five children who received hospice or no interventions as their highest level of intervention (6.1%) (no necessary or aggressive interventions provided). The median survival in months for children receiving hospice or no interventions as their highest level of care and still living at time of survey completion was 252 months, which was due to a large survival range as noted below. The mean survival time for those still living was 204 months. The median survival time for those deceased at time of survey completion in this group was 8.5 months. The survival range for those still living at time of survey completion was 353 months. The survival range for those deceased at time of survey completion was 5 months (same as above). The 1-year survival (those children who were 1 year or older) was 40% (n = 5).

Necessary interventions

Forty-six children received necessary interventions including enteral feeding and use of a ventilator (56.1%) as their highest level of intervention. The median survival time for those receiving necessary interventions as their highest level of care and still living at time of survey completion was 57 months. The mean survival time for those in this group was 88.64 months. The median survival time for those deceased at time of survey completion was 8 months. The mean survival time for those in this group was 43.7 months. The survival range for those still living at time of survey completion was 381 months. The survival range for those deceased at time of survey completion was 300 months. The 1-year survival was 71.7% (n = 31).

Aggressive interventions

There were 31 children who received aggressive interventions including surgery for cardiac and respiratory issues (37.8%) as their highest level of

TABLE I. Demographic Data at Time of TRIS Survey Completion (n = 82)

	Mean, Median (±SD) Range
Child's age in months (n = 59) (living at time of completion)	70, 48 (±86.43) Range: 3–394
Child's age in months (n = 24)[a] (passed away by time of completion)	53.4, 9[b] (±88.51) Range: 2–301
Marital status	n (%)
Single	5 (6.1)
Long term relationship	2 (2.4)
Married	70 (85.4)
Separated	3 (3.7)
Divorced	2 (2.4)
Education level	
Less than 6 years	1 (1.2)
7–9 years	1 (1.2)
10–12 years	17 (20.7)
13–16 years	31 (37.8)
17–20 years	25 (30.5)
More than 20 years	7 (8.5)
Income level[c]	
Low	10 (12.2)
Medium	65 (79.3)
High	7 (8.5)

[a]Participant only responded to this demographic item (n = 83 total).
[b]Median low due to skewed distribution.
[c]Income level is not described in dollar amounts due to the international scope of the project.

intervention in this study. The median survival time for those receiving aggressive interventions as their highest level of care and still living at time of survey completion was 45 months. The mean survival time for this group was 49.2 months. The median survival time for those deceased at time of survey completion was 13.5 months. The mean survival time for those in this group was 60.69 months. The survival range for those still living at time of survey completion was 152 months. The survival range for those deceased at time of survey completion was 256.5 months. The 1-year survival was 80.6% (n = 46).

Forty of 82 children received surgery (48.8%, i.e., surgery for placement of feeding tube, these surgeries are not all considered aggressive interventions) and 15 of 40 received aggressive interventions regarding respiratory issues (18.3%), while 22 of 40 received aggressive interventions regarding cardiac issues (26.8%).

Highest Level of Intervention and Survival

Of the children receiving necessary interventions as their highest level of intervention, 33 were still living at the time of survey completion (71.7%). In addition, of the children receiving aggressive interventions as their highest level of intervention, 23 were still living at the time of the survey completion (74.2%). Table II provides additional information.

Gender and Interventions

Three males (37.5%) and 28 females (48.3%) received hospice care. In the case of surgery, male and female percentages were nearly equal. Seven males (50%) and 33 females (48.5%) underwent surgery. Additionally, the overall percentage of males with enteral feeding was 85.7% (n = 12), which was similar to females (n = 61, 89.7%) (see Table III).

DISCUSSION

In a sample of 82 children, few received hospice as their highest level of intervention (n = 5, 6.1%). More specifically, approximately half the sample (n = 46, 56.1%) received necessary interventions such as some form of enteral feeding as their highest level. Thirty-one children (37.8%) received aggressive interventions and a majority was still living at the time of survey completion (n = 23, 74.2%). In addition, overall, a high percentage of the sample was living at time of survey completion (n = 59, 72%), which is in contrast with most available literature. The overall percentage of males and females that received aggressive interventions were similar with 50% of males receiving surgery and 48.5% of females

TABLE II. Highest Level of Intervention[a] and Survival (n = 82)

	Status at time of survey completion	
	Living n (%)	Deceased n (%)
Hospice care or no interventions (n = 5)	3 (60)	2 (40)
Necessary interventions (n = 46)	33 (71.7)	13 (28.3)
Aggressive interventions (n = 31)	23 (74.2)	8 (25.8)

[a]Categories are based upon highest level of care provided. For example, those who have received hospice have not received necessary or aggressive interventions and those who have received necessary interventions did not receive aggressive interventions.

receiving surgery. The overall percentage of males and females that received enteral feeding was also similar with 85.7% of males and 89.7% of females.

Thirty-one children (37.8%) received aggressive interventions and a majority was still living at the time of survey completion (n = 23, 74.2%). In addition, overall, a high percentage of the sample was living at time of survey completion (n = 59, 72%), which is in contrast with most available literature.

The 1-year survival for those children receiving no interventions as their highest level of care was 40% (n = 5) and the 1-year survival for those children receiving necessary interventions as their highest level of care was 71.7% (n = 31) with the 1-year survival for those children receiving aggressive interventions as their highest level of care as 80.6% (n = 46), respectively. This trend suggests that 1-year survival increased as more aggressive interventions were used.

These descriptive results from a large sample align with some current literature and anecdotal reports from parents [e.g., Janvier and Watkins, 2013]. Specifically, data presented here showed a large percentage of survivors (n = 59, 72%) including those receiving aggressive interventions (n = 23, 74.2%), which shows that aggressive interventions may impact survival as opposed to some literature that does not advocate for their use [Boss and Broers, 1992; Goc et al., 2006; Li and Liu, 2012]. Results also suggest that the sample described here from the TRIS project database may have included parents who advocate and request aggressive interventions, for their children in greater numbers than previously reported.

Highest level of intervention was considered. If a child received hospice and no other interventions, hospice would be considered the highest level of care or no intervention. If a child received necessary interventions and no other higher level of interventions such as aggressive interventions, the child would have necessary intervention as the highest level of care. Lastly, a child that received aggressive interventions received the highest level of care to include surgery. For highest level of interventions, five children (60% of those five still living) received hospice care, which was considered *no intervention* in this study while 46 (71.7% of those 46 still living) received necessary interventions as their highest level of intervention, and 31 (74.2% of those 31 still living) received aggressive interventions as their highest level of intervention. This was consistent with

TABLE III. Gender and Interventions[a] (n = 82)

	Male (n = 14)		Female (n = 68)		Aggregate (n = 82)	
	Yes n (%)	No n (%)	Yes n (%)	No n (%)	Yes n (%)	No n (%)
Hospice (n = 31)	3 (37.5)	5 (62.5)	28 (58.3)	20 (41.7)	31 (55.4)	25 (44.6)
Necessary intervention						
Enteral feeding (n = 73)	12 (85.7)	2 (14.3)	61 (89.7)	7 (10.3)	73 (89.0)	9 (11.0)
Ventilator (n = 32)	7 (58.3)	5 (41.7)	25 (38.5)	40 (61.5)	32 (41.6)	45 (48.4)
Aggressive intervention						
Surgery (n = 40)	7 (50.0)	7 (50.0)	33 (48.5)	35 (51.5)	40 (48.8)	42 (51.2)

[a]Multiple interventions have been used for individual children. Table does not represent highest level of intervention. For example, a child that utilized aggressive interventions such as surgery may have also received necessary interventions such as enteral feeding.

existing research that has shown a higher survival rate when children are provided with aggressive medical interventions such as cardiac surgery [Kosho et al., 2006; Kaneko et al., 2008; Kobayashi et al., 2010]. Recently published, Nelson et al. (2016) emphasizes this point as well.

While there were less males represented than females, the percentage of males (85.7%) and females (89.7%) receiving necessary such as enteral feeding and/or aggressive interventions such as surgery for males (50%) and females (48.5%) was similar. Further, results showed 50% of males living at the time of survey completion and 76.5% of females living at time of survey completion despite the similar use of interventions as stated above. This is in line with current literature consistently identifying a lower survival rate for males with full t18 than females with full t18 [Hsaio et al., 2009; Rosa et al., 2011; Wu et al., 2013].

Limitations

A number of limitations affected the results. First, the TRIS Survey is a retrospective, parent-reported survey. Parent report may be affected by a number of factors including passage of time and unfamiliarity with terms used for specific medical interventions. Responses may not be fully accurate. When the survey was developed, items were not specifically included for the hospice care option, only a general question about its provision. The resulting data is incomplete due to variation in what is considered hospice care. A "Yes" or "No" response does not provide insight into participants' hospice experiences (e.g., length of time, services provided).

This type of database also holds the potential for selection bias. Enrollment and participation in the TRIS project could be affected by children's longevity and continued positive outcomes to intervention (necessary and/or medical). In addition, while the available literature emphasizes female longevity [Niedrist et al., 2006; Cereda and Carey, 2012], it is unclear why the sample included so few males. Conclusions cannot be projected or drawn with any certainty.

In addition, since the third author is the project's principal investigator, the decision was made to only provide the first author with access to requested data. Parent contact information was not shared, which affected the third author's ability to communicate with participants who did not complete all needed survey items.

Implications

As described elsewhere, aggressive and necessary medical interventions may contribute to longevity for children with t18 [Bruns and Martinez, 2016]. Without additional research, causality cannot be determined but it is important to consider interventions of this type when a child is determined to be stable enough for surgery, for example. In addition, if only hospice care are initially offered, additional interventions should not be ruled out. Until there is more evidence of which medical needs differentiate a long-term survivor, limiting or withholding care should not be made on the basis of a diagnosis.

There is also a need to provide members of a child's care team with up-to-date information on t18. Available literature varies in emphasis on mortality data, case study descriptions and successful interventions [e.g., Kosho et al., 2006; Breeze et al., 2007; Merritt et al., 2012; Bruns and Campbell, 2014; Lorenz and Hardart, 2014]. While many children may not respond positively to some or all necessary or aggressive medical interventions, it, again, does not rule out their discussion. This is especially critical in providing parents with balanced information on benefits and risks of all possible interventions [Guon et al., 2014]. Decision-making should be viewed as a process rather than, largely, a forgone conclusion based on what may be inaccurate information.

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Bruns [2013] offers the following perspective, "...recommendations for their care can be made on an informed basis rather than from a biased perspective inclined toward comfort care or palliative care." [p. 3]. In keeping with the results presented here, the availability of necessary and/or aggressive interventions may impact survival. Parents should be presented with all types of available interventions and provided with the opportunity to provide their input and perspective on what is best for the care of their children.

Medical professionals can use data offered here to describe the need for interventions such as enteral feeding and surgeries to correct specific conditions common among children with t18. Specifically, genetic counselors could share the information from this study with parents receiving a prenatal diagnosis of t18 as a guide for dialogue about care options. This is important as the grim prognosis and use of terms such as *lethal* can have a dramatic influence on the decisions parents make regarding the type of medical intervention their children should receive after birth [Gessner, 2003; McGraw and Perlman, 2009; Guon et al., 2014]. Data presented here yielded descriptive results that can facilitate for continued discussion among caregivers, medical professionals, and families of children with t18.

Future Research

Future research could include qualitative data from interviews with parents of children with t18 to discuss the impact

of various interventions. Longitudinal data could be collected and analyzed over several years (or longer) to track additional surgeries and the like. The TRIS project collects such data. Examples including a minimum of 3 years data can be found at the project's case studies page located at http://tris.siu.edu/case-studies/index.html

Additional research could utilize data from the TRIS project survey to examine variables regarding specific medical interventions such as specific surgeries with quantitative analyses such as a logistic regression analysis. This may be the most realistic approach since the data already exists to perform this analysis; it is also thought, after conducting this study, that a logistic regression analysis may be more closely aligned to some of the descriptive results Similar analyses can be completed with children with other rare trisomy conditions such as trisomy 13, trisomy 9 mosaic, and trisomy 8 mosaic to examine occurrence of necessary interventions and aggressive medical interventions. In addition, comparative analyses could be performed across children with various trisomy types such as full trisomy 18, trisomy 18 mosaic, and partial trisomy 18.

CONCLUSION

In conclusion, the findings reported here describe evidence for greater provision of necessary and aggressive medical interventions for children with t18. It is hoped that perceptions regarding children with t18 will become more positive and interventions more widely offered and provided to this group.

REFERENCES

Bos AP, Broers CM. 1992. Avoidance of emergency surgery in newborn infants with trisomy 18. Lancet 339:913–915.

Boss AP, Broers CJM. 1992. Avoidance of emergency surgery in newborn infants with trisomy 18. Lancet 39:913–917.

Breeze A, Lee C, Kumar A, Missfelder-Lobos H, Murdoch E. 2007. Palliative care for the prenatally diagnosed lethal fetal abnormality. Arch Dis Child Educ Pract Ed 92:F56–F58.

Bruns DA. 2008. Pregnancy and birth history of newborns with trisomy 18 or 13: A pilot study. Am J Med Genet A 146:321–326.

Bruns D. 2013. Erring on the side of life: Children with rare trisomy conditions, medical interventions and quality of life. J Genet Disord Genet Rep 2:1–5.

Bruns D, Campbell E. 2014. Twenty-two survivors over the age of 1year with full trisomy 18: Presenting and current medical conditions. Am J Med Genet 164A:610–619.

Bruns D. 2015. Developmental status of 22 children with trisomy 18 and eight children with trisomy 13: Implications and recommendations. Am J Med Genet 167A:1807–1815.

Bruns DA, Martinez A. 2016. An analysis of cardiac defects and surgical interventions in 84 cases with full trisomy 18. Am J Med Genet 170A:337–343.

Cereda A, Carey JC. 2012. The trisomy 18 syndrome. Orphanet J Rare Dis 7:81–95.

Everett B, Albersheim S. 2011. Ethical care for infants with conditions not curable with intensive care. J Clin Ethics 22:54–60.

Gessner BD. 2003. Reasons for trisomy 13 or 18 births despite the availability of prenatal diagnosis and pregnancy termination. Early Hum Dev 73:53–60.

Goc B, Walenka Z, Wloch A, Wojciechowska E, Wiecek-Wlodarska D, Krzystolik-Ladzinska J, Swietlinski J. 2006. Trisomy 18 in neonates: Prenatal diagnosis, clinical features, therapeutic dilemmas and outcome. J Appl Genet 47:165–170.

Guon J, Wilfond BS, Farlow B, Brazg T, Janvier A. 2014. Our children are not a diagnosis: The experience of parents who continue their pregnancy after a prenatal diagnosis of trisomy 13 or 18. Am J Med Genet 164A:308–318.

Hentschel R, Lindner K, Krueger M, Reiter-Theil S. 2006. Restriction of ongoing intensive care in neonates: A prospective study. Pediatr 18:563–569.

Hsiao C, Tsao L, Chen H, Chiu H, Chang W. 2009. Changing clinical presentations and survival pattern in trisomy 18. Ped Neonat 50:147–151.

Janvier A, Watkins A. 2013. Medical interventions for children with trisomy 13 and trisomy 18: What is the value of a short disabled life? Acta Paediatr 102:1112–1117.

Janvier A, Farlow B, Wilfond B. 2012. The experience of families with children with Trisomy 13 and 18 in the social networks. Pediatr 130:293–298.

Kaneko Y, Kobayashi J, Yamamoto Y, Yoda H, Kanetaka Y, Nakajima Y, Kawakami T. 2008. Intensive cardiac management in patients with trisomy 13 or trisomy 18. Am J Med Genet 146A:1372–1380.

Kobayashi J, Kaneko Y, Yamamoto Y, Yoda H, Tsuchiya K. 2010. Radical surgery for a ventricular septal defect associated with Trisomy 18. Gen Thorac Cardiovasc Surg 58:223–227.

Kosho T. 2008. Care of children with trisomy 18 in Japan. Am J Med Genet 146A:1369–1371.

Kosho T, Kuniba H, Tanikawa Y, Hashimoto Y, Sakurai H. 2013. Natural history and parental experience of children with trisomy 18 based on a questionnaire given to a Japanese trisomy 18 parental support group. Am J Med Genet 161A:1531–1542.

Kosho T, Nakamura T, Kawame H, Baba A, Tamura M, Fukushima Y. 2006. Neonatal management of trisomy 18: Clinical details of 24 patients receiving intensive treatment. Am J Med Genet 140A:937–944.

Lakovschek IC, Streubel B, Ulm B. 2011. Natural outcome of trisomy 13, trisomy 18, and triploidy after prenatal diagnosis. Am J Med Genet 155A:2626–2633.

Li D, Liu H. 2012. Prenatal diagnosis of trisomy 18: Report of 76 cases in a mainland Chinese hospital. J Matern Fetal & Neonatal Med 25:2144–2144.

Lorenz JM, Hardart GE. 2014. Evolving medical and surgical management of infants with trisomy 18. Curr Opin Pediatr 26:169–176.

Maeda J, Yamagishi H, Furutani Y, Kamisago M, Waragai T, Oana S, Nakanishi T. 2011. The impact of cardiac surgery in patients with trisomy 18 and trisomy 13 in Japan. Am J Med Genet 155A:2641–2646.

McGraw MP, Perlman JM. 2008. Attitudes of neonatologists toward delivery room management of confirmed trisomy 18: Potential factors influencing a changing dynamic. Pediatrics 121:1106–1110.

McGraw M, Perlman J. 2009. Attitudes of neonatologists toward delivery room management of confirmed trisomy 18: Potential factors influencing a changing dynamic. Pediatr 121:1106–1110.

Merritt T, Catlin A, Wool C, Peverini R, Goldstein M, Oshiro B. 2012. Trisomy 18 and trisomy 13: Treatment and management decisions. Neo Rev 13:e40–e48.

Nelson KE, Rosella LC, Mahant S, Guttmann A. 2016. Survival and surgical interventions for children with trisomy 13 and 18. JAMA 316:420–428.

Niedrist D, Riegel M, Achermann J, Rousson V, Schinzel A. 2006. Trisomy 18: Changes in sex ratio during intrauterine life. Am J Med Genet 140A:2365–2367.

Pruszewicz A, Wiskirska-Woznica B, Wojnowski W, Czerniejewska H, Jackowska J, Leszczynska M. 2014. Phenotype-genotype discordance in congenital malformations with communication disorders resembling trisomy 18 (Edwards syndrome). Am J Case Rep 15:41–44.

Rasmussen SA, Wong LC, Yang Q, May KM, Friedman JM. 2003. Population-based analyses of mortality in trisomy 13 and trisomy 18. Pediatr 111:777–784.

Rosa RFM, Rosa RCM, Lorenzen MB, de Moraes FN, Graziadio C, Zen PRG, Paskulin GA. 2011. Trisomy 18: Experience of a reference hospital from the south of Brazil. Am J Med Genet 155:1529–1535.

Romesberg T. 2007. Building a case for neonatal palliative care. Neonatal Netw 26:111–115.

Showalter S. 2009. Attitudes of neonatologists toward delivery room management of confirmed trisomy 18: Potential factors influencing a changing dynamic. Pediatrics 123: e548–e549.

Watkins A. 2011. Commentary on 'going against the grain: 'Liam's story.' J Paediatr Child Health 47:659–660.

Wu J, Springett A, Morris JK. 2013. Survival of trisomy 18 (Edwards syndrome) and trisomy 13 (Patau syndrome) in england and wales: 2004–2011. Am J Med Genet 161:2512–2518.

Yates AR, Hoffman TM, Shepherd E, Boettner B, McBride KL. 2011. Pediatric sub-specialist controversies in the treatment of congenital heart disease in trisomy 13 or 18. J Genet Counsel 20:495–509.