Inpatient Hospital Care of Children With Trisomy 13 and Trisomy 18 in the United States

WHAT’S KNOWN ON THIS SUBJECT: Trisomy 13 and trisomy 18, common chromosomal abnormalities, are generally considered fatal within the first year after birth, although some children live longer. Little is known, however, about the inpatient medical courses of these infants and children.

WHAT THIS STUDY ADDS: Evaluation of nationally representative hospitalization data demonstrates that a significant number of children with trisomy 13 and trisomy 18 live beyond 1 year of age and that the care they receive includes both medical and surgical treatments.

abstract

BACKGROUND AND OBJECTIVE: Trisomy 13 and trisomy 18 are generally considered fatal anomalies, with a majority of infants dying in the first year after birth. The inpatient hospital care that these patients receive has not been adequately described. This study characterized inpatient hospitalizations of children with trisomy 13 and trisomy 18 in the United States, including number and types of procedures performed.

METHODS: Retrospective repeated cross-sectional assessment of hospitalization data from the nationally representative US Kids’ Inpatient Database, for the years 1997, 2000, 2003, 2006, and 2009. Included hospitalizations were of patients aged 0 to 20 years with a diagnosis of trisomy 13 or trisomy 18.

RESULTS: The number of hospitalizations for each trisomy type ranged from 846 to 907 per year for trisomy 13 (P = .77 for temporal trend) and 1036 to 1616 per year for trisomy 18 (P < .001 for temporal trend). Over one-third (36%) of the hospitalizations were of patients older than 1 year of age. Patients underwent a total of 2765 major therapeutic procedures, including creation of esophageal sphincter (6% of hospitalizations; mean age 23 months), repair of atrial and ventricular septal defects (4%; mean age 9 months), and procedures on tendons (4%; mean age 8 years).

CONCLUSIONS: Children with trisomy 13 and trisomy 18 receive significant inpatient hospital care. Despite the conventional understanding of these syndromes as lethal, a substantial number of children are living longer than 1 year and undergoing medical and surgical procedures as part of their treatment. Pediatrics 2012;129:869–876

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KEY WORDS: child health services, chronic conditions, cohort studies, congenital abnormalities/anomalies, delivery of care

ABBREVIATIONS: CCS—Clinical Classification Software; HCUP—Healthcare Cost and Utilization Project; ICD-9-CM—International Classification of Diseases, Ninth Revision, Clinical Modification; KID—Kids’ Inpatient Database.

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The most common chromosomal abnormalities noted in live-born infants are trisomy 21, trisomy 18, and trisomy 13. Of these, trisomies 13 and 18 have generally been considered fatal anomalies, as a majority of infants have typically died in the first year after birth. The syndromes are associated with defects in multiple systems including cardiovascular lesions, central nervous system anomalies, gastrointestinal and abdominal wall defects, among others.1

The first descriptions of trisomy 13 and trisomy 18 appeared in the literature in 1960,2,3 Two 1966 case series evaluated survival in these syndromes. The trisomy 13 report described 8 cases with a mean survival time of 61 days.4 In the case series of 17 patients cases with a mean survival time of 61 days, the authors found a preponderance of girls (59%) and a mean survival of 190 days.5 Later studies reveal shorter mean survival times; articles in 1994 and 1996 revealed mean survival times of 4 days and 3 days, respectively.6,7 A 2002 population-based study in Scotland from 1974 to 1997 revealed no significant change in the mean survival time of infants born with trisomy 13 (8.5 days) or trisomy 18 (6 days) during the 3-decade study period; the authors explained the unchanging duration of survival as secondary to central apnea as a difficult-to-prevent cause of death.8 Other long-term population-based studies have similar findings,9 with variation only noted in short-term survival over the past 40 years.10,11 Improvements in prenatal diagnosis may lead to increased identification of cases; however, in a recent retrospective review of 34 prenatally diagnosed cases, only 4 of the 14 cases in which the family chose to continue the pregnancy survived to delivery, and all died within 11 days after birth.12

Though mean survival time for both syndromes is generally thought to be on the order of days, both the population studies and multiple case reports identify some long-term survivors.13,14 Mosaicism has been suggested as a possible mechanism for these cases,15 but there is poor correlation between the ratio of mosaic to normal cells, the degree of phenotypic characteristics, and survival in either trisomy 13 or trisomy 18.16–18 Although some children with mosaic trisomy 13 or trisomy 18 do live longer,19,20 many of the reported cases of long survival for children with trisomy 13 or trisomy 18 are specifically noted to be full trisomies.14,21 A recent study, which collected information from parents of 30 children with full trisomy 13 who survived longer than 60 days, revealed a mean age of 48 months (range 2–167 months) among the 18 children alive at time of data collection.22 A related study of 23 children with full trisomy 18 revealed a mean age of 103 months (range 3–394 months) for the living cohort of 13 children.23 At this time, what accounts for this small, but clearly existent, group of long-term survivors with trisomy 13 and trisomy 18 remains unclear.

Much of the descriptive literature about children with trisomy 13 and 18 is in the form of case series reports. These studies often include a limited amount of information about the infants’ medical courses, and practices vary broadly across different countries and sites. There are signs, however, of a shift toward a new era of providing life-prolonging medical interventions. In a 22-year retrospective study in England from 1985 to 2007, none of 67 live-born infants with trisomy 18 and only 2 of 50 infants with trisomy 13 underwent surgeries, 1 for cleft lip and palate and 1 for aortic coarctation.9 In a 1994 case series drawn from parental support group reports, 13% of 98 trisomy 18 patients and 23% of 32 trisomy 13 patients had surgery in the neonatal period, primarily involving repairs of the gastrointestinal tract.24 Several articles from Japan in the early 2000s explored the effect of increasing interventions. A case series of 31 infants with trisomy 13 and 18 in Japan during a time of changing availability of cardiac surgery between 2000 and 2005 revealed operative interventions including 4 gastrointestinal, 4 cardiac, 2 neurosurgical, 1 genitourinary, and 1 airway procedures.25 A case series of 24 infants in Japan with trisomy 18 published in 2006 evaluating the effects of intensive NICU management revealed 1 palliative cardiac surgery and 20 noncardiac surgeries (gastrointestinal and airway).26 The transition in style of care was not limited to Japan: a Polish case series in 2006 of 20 aggressively managed neonates with trisomy 18 revealed 9 total surgeries, 4 of which were cardiac.27 There continues to be, though, wide variation in practice: in a case series of 31 infants with trisomy 18 in Taiwan published in 2009, no infants underwent surgery during the neonatal period.28 The authors of a recent article explored the complex and controversial ethics of decision-making and provision of treatment of patients with trisomy 18.29

We therefore sought to use a multiyear national database containing a representative sample of inpatient discharge data to evaluate the medical and surgical inpatient care that children with trisomy 13 and trisomy 18 receive in the United States and examine trends over time.

METHODS

Data Source

We used the Kids’ Inpatient Database (KID), a database within the Healthcare Cost and Utilization Project (HCUP) sponsored by the Agency for Healthcare Research and Quality for the years 1997, 2000, 2003, 2006, and 2009. The database contains discharge abstract
data from pediatric inpatient hospital admissions, including variables such as age at admission, diagnoses (up to 15 per admission), procedures performed (up to 15 per admission), and length of stay. Diagnoses and procedures were coded by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) system. The database is designed to include 80% of administrative hospital discharge reports for complicated in-hospital births and other admissions, as well as 10% to 20% of uncomplicated births. The KID encompasses data for a plurality of states for each of the data years. The number of included states has increased for each subsequent data-year, from 22 states in 1997 to 44 states in 2009. The database is weighted to allow calculation of national estimates. Pediatric admissions are defined as patients 18 and younger at time of admission in 1997 data and 20 and younger at time of admission in 2000 and later data. Additional information about the KID database is available from http://www.hcup-us.ahrq.gov/kidoverview.jsp, accessed November 14, 2011.

Data Analysis
We used ICD-9-CM diagnosis codes to extract from the KID all discharge documentation for hospitalizations with trisomy 13 (758.1) or trisomy 18 (758.2) listed as a diagnosis in years 1997, 2000, 2003, 2006, and 2009. Hospitalizations that included maternal data were excluded from the analysis. Discharge-specific weights were used to create national estimates from the data. Ages at admission were grouped into the following categories: <1 year, 1 to 2 years, 3 to 7 years, and 8+ years. Hospital regions were assigned according to the geographic regions on the US Census Bureau map. A tool created by HCUP to divide procedures and diagnoses into clinically relevant groups for research analysis was used to create national estimates from the data in the KID. Outcomes data were assessed by linear regression to evaluate for significance of trends over time.

RESULTS

Demographic Characteristics
The girl-to-boy ratio was approximately equal for trisomy 13 (52% girls) and was greater for trisomy 18 (64% girls), which is consistent with previous studies (Table 1). With the exception of the designated primary payer, none of the patient demographic data changed significantly over time for trisomy 13 (data not shown). Among discharges of children with trisomy 18, there were statistically significant shifts over time in primary payer and admission type, although because of inter-year variability there were no

<table>
<thead>
<tr>
<th>Gender</th>
<th>Trisomy 13, N = 4308</th>
<th>Trisomy 18, N = 6630</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>P*</td>
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<tr>
<td></td>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Girl</td>
<td>2248 (52.2)</td>
<td>.87</td>
</tr>
<tr>
<td>Boy</td>
<td>2057 (47.7)</td>
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</tr>
<tr>
<td></td>
<td>Hospital region</td>
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</tr>
<tr>
<td>Northeast</td>
<td>509 (17.3)</td>
<td>.36</td>
</tr>
<tr>
<td>Midwest</td>
<td>663 (19.1)</td>
<td></td>
</tr>
<tr>
<td>South</td>
<td>1351 (39.0)</td>
<td></td>
</tr>
<tr>
<td>West</td>
<td>850 (24.5)</td>
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<tr>
<td></td>
<td>Primary payer</td>
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<tr>
<td>Private</td>
<td>1976 (45.9)</td>
<td>&lt;.001</td>
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<tr>
<td>Medicaid</td>
<td>2029 (47.1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>294 (6.8)</td>
<td></td>
</tr>
<tr>
<td>Birth visit</td>
<td>Yes</td>
<td>1262 (29.5)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>3047 (70.7)</td>
</tr>
<tr>
<td>Admission type</td>
<td>Urgent/emergent</td>
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<tr>
<td></td>
<td>Elective</td>
<td>436 (10.1)</td>
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<tr>
<td></td>
<td>Newborn</td>
<td>1103 (25.8)</td>
</tr>
<tr>
<td></td>
<td>Other/missing</td>
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</tr>
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<td>2558 (59.4)</td>
<td>.29</td>
</tr>
<tr>
<td>1–2</td>
<td>602 (14.0)</td>
<td></td>
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<tr>
<td>3–7</td>
<td>502 (11.8)</td>
<td></td>
</tr>
<tr>
<td>≥8</td>
<td>645 (15.0)</td>
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</tr>
</tbody>
</table>

* Reported P values evaluate for differences in trends over time for categories of each variable, tested separately for each trisomy.

b Regional data not available for 1997, thus those admissions were not included in this category.

c Other includes Medicare, self-pay, no-charge and other.

d Missing admission type data creates the seeming discrepancy between number of birth visits and number of newborn admissions.
clear trends (data not shown). Considered in aggregate, slightly less than half of admissions were covered by private insurance, and Medicaid covered a similar percentage. In both trisomy 13 and trisomy 18, approximately two-thirds of visits were nonbirth admissions, with trisomy 18 demonstrating a higher total percentage of birth visits. Concurrently, the percentage of urgent/emergent admissions for trisomy 18 was lower. Children >1 year of age represent 36% of discharges. Figure 1 depicts the number of hospitalizations of children greater than age 1 over time.

**Hospitalizations and Discharge Dispositions**

Between 1997 and 2009, as shown in Table 2, the number of admissions of children with trisomy 13 ranged from 846 to 907, which was not a significant change over time. Admissions for trisomy 18 did significantly increase during the study years, from 1036 to 1615 ($P < .001$) compared with annual total of US births for the study years.33,34 One-third of the total hospitalization records represent birth admissions and 46% of those admissions were discharged alive. Length of stay and frequency of death during admission remained stable during the observation period for trisomy 13. For trisomy 18, overall length of stay increased, though not quite significantly, with the proportion of admissions lasting $\geq$3 weeks nearly doubling. The frequency of in-hospital deaths decreased significantly for trisomy 18. Disposition of patients who survived to discharge was stable for trisomy 13 but changed significantly for trisomy 18. Notably, the percentage of discharges to home health care, a category including hospice, more than doubled during the observation period (Table 2).

**FIGURE 1**
Total number of inpatient hospitalizations of children with trisomy 13 or trisomy 18 who are over 1 year of age at the time of admission for 1997 and 2009.

**TABLE 2** Temporal Trends of Trisomy 13 and Trisomy 18 Hospitalization Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Trisomy 13</th>
<th>Trisomy 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of admissions</td>
<td>846</td>
<td>841</td>
</tr>
<tr>
<td>Death during admission, %a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>24.7</td>
<td>27.5</td>
</tr>
<tr>
<td>No</td>
<td>75.3</td>
<td>72.5</td>
</tr>
<tr>
<td>Disposition of surviving patients, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Routine</td>
<td>71.7</td>
<td>70.9</td>
</tr>
<tr>
<td>Facility</td>
<td>17.4</td>
<td>15.5</td>
</tr>
<tr>
<td>Home health</td>
<td>10.6</td>
<td>13.2</td>
</tr>
<tr>
<td>Mean length of stay, d</td>
<td>6.55</td>
<td>8.12</td>
</tr>
<tr>
<td>Mean age at admission, y</td>
<td>2.50</td>
<td>2.17</td>
</tr>
</tbody>
</table>

*In 1997 data only, an out-of-hospital death is counted as death during admission.*
Diagnoses and Procedures

The total number of major therapeutic procedures increased over time, though not significantly (Fig 2). The number of diagnoses and procedures per admission also increased for both types of trisomy over the observation period, with statistical significance achieved except in procedures for trisomy 18, which neared significance with a P value of .06 (Fig 3). Most admissions included 5 or fewer procedures, with 43% of records listing no procedures and 47% listing 1 to 5 procedures. The percentage of records with more than 10 procedures was ~1% for both trisomies. The age at time of major therapeutic intervention is varied: 46% of major therapeutic interventions occur in children <1 year of age, 17% from 1 to 2 years, 14% from 3 to 7 years, and 23% in children older than 8 years. During the observation years, there were 2765 major therapeutic procedures performed on children with trisomy 13 and trisomy 18. Table 3 delineates the top 5 procedure types by CCS category, listing the most frequent specific surgeries in each category as well as presenting data for tracheotomies. Approximately 9% of major therapeutic procedures involved the upper gastrointestinal tract. Of these procedures, the most common was creation of esophageal sphincter competence, as is performed in gastric fundoplication operations. Cardiac procedures were less common in children with trisomy 13 compared with trisomy 18. The mean admission age of children undergoing cardiac procedures was lower than any other procedure category: 1.2 years for children with trisomy 13 and 0.7 years among children with trisomy 18. A majority of the cardiac procedures involved repair of atrial septal defects and ventricular septal defects, although a small number of children underwent repair of truncus arteriosus and Tetralogy of Fallot. Tracheotomy represented 3% of the total major therapeutic procedures performed in children with trisomy 13 and 5% of procedures on children with trisomy 18.

**DISCUSSION**

This study of national data demonstrates that children with trisomy 13 and trisomy 18 receive significant inpatient medical care. Although previous case studies reveal mean survival times in terms of days, in our study, one-third of the 10 939 hospitalization records represent birth admissions and 46% of those admissions were discharged alive after a mean stay of 7.8 days. Of note, although general estimates of 1-year
survival are less than 10%, we identified that 41% and 32% of the hospital records were of children over 1 year of age with trisomy 13 and 18, respectively. Further, in >10% of discharges, the child was over the age of 8 years at time of admission. Additionally, these children received many medical interventions; over 2500 major therapeutic procedures during the 5 observation years. With the exception of cardiac intervention in children with trisomy 18, the mean ages at which procedures were performed in the other categories were >1 year.

The types of interventions children received did not necessarily correlate with the prevalence of defect types in these trisomic populations. A study in 2006 quantified the frequency of defects by using, in part, data from the KID database: among infants with trisomy 18, 45% had heart defects and 7% had tracheo-esophageal fistula, and 4% had cleft lip; among infants with trisomy 13, 35% had heart defects, 25% had orofacial anomalies, and 21% had defects in the abdominal wall. Although the cardiac defects were the most common for both trisomies, cardiac procedures accounted for only 6% of the major procedures identified in this study. There is some suggestion that the frequency of cardiac interventions for children with trisomy 18 is increasing; 47 of the total 120 procedures (40%) were performed in 2009 alone. Though on smaller scale, the previously published studies described above are similar regarding the relative underrepresentation of cardiac procedures9, 24–27, which may reflect the risk-benefit ratio of cardiac procedures compared with other interventions, such as gastrostomy tube placement. Previous studies have also debated the lethality of cardiac defects associated with trisomy 13 and trisomy 186,7,11, which may impact the rate at which intervention is deemed necessary. Interestingly, given the controversy surrounding life-sustaining interventions in this population, tracheotomies represented 5% of major therapeutic procedures in trisomy 18 and 3% in trisomy 13.

The findings of this study need to be interpreted with an important caveat. Although this utilizes data from a large, nationally representative data source (and thus eliminates selection bias, which potentially compromises case series reports), the data represent hospitalizations rather than individuals. At a minimum, based on birth visits, the sample includes 1262 children with trisomy 13 and 2380 with trisomy 18; however, it is not possible to extrapolate the specific number of children represented in the sample of 4309 and 6630 admissions of children with trisomy 13 and 18, respectively.

A relatively smooth distribution of ages within each data year suggests against, but does not exclude, a small cohort of patients who are admitted to the hospital multiple times each of the study years. Further, the procedural data are likely less impacted by such an issue: although some major operative procedures require revisions over time, most major procedures would occur no more frequently than once per year for an individual child. The data in the KID is de-identified in a manner that precludes linkage and evaluation of an individual child’s hospitalization experiences over time and thus limits the ability to assess whether more frequent interventions are associated with longer survival. Older children do, however, appear to receive more interventions; though accounting for only 12% of admissions, children over 8 years of age underwent 23% of major therapeutic procedures.

The distribution of admission ages found in this study is significantly different than the commonly assumed natural history would suggest. Because the data were selected based on ICD-9-CM codes for trisomies in an administrative database, there is an unquantifiable risk of primary miscoding or misdiagnosis causing improper identification of discharge data. Many of the studies that reveal natural histories of these syndromes, however, are series containing 200 or fewer cases per trisomy, and often far fewer.4–10,14,24,28,35,36 Though most of these studies reveal a relatively smooth distribution of ages within each data year, extrapolating these data to larger populations is fraught with potential bias, and the cumulative total number of long-term survivors is unknown. One large population-based study revealing data from US birth certificates linked to death certificates included 5515 cases with trisomy 13 and 8750

![Figure 3](image-url)
with trisomy 18, but this study did not reveal the survival curve for older patients beyond noting that 6% of cases survive longer than 1 year. Despite these previous studies have revealed the average age of patients at the time of death, in our study, the age distribution of hospitalizations is likely more reflective of the prevalence of individuals living with trisomy 13 and 18, which will be older. Additionally, although mosaicism has at best an unclear effect on survival, no discharges in the KID database contain the ICD-9-CM code for mosaicism (758.91), so it is not possible to do a subanalysis to evaluate potential effect. Previously reported interventions in trisomy 13 and 18 populations varied widely in both frequency and type, with multiple case series not including any reports of surgical interventions. To the degree that a uniform "nonintervention" paradigm ever existed in the past, though, the patterns of care over the past decade and a half suggest that such a paradigm is no longer universal. This study reveals that in the United States, a significant number of children with trisomy 13 and 18 undergo surgical procedures as part of their inpatient medical care. The frequency with which these interventions are done is increasing and may or may not be associated with the noted trends for decreased frequency of in-hospital death, increased disposition to home health, and increased mean admission age seen in patients with trisomy 18. Although much attention in the literature has been paid to cardiac procedures, compared with other types of interventions, cardiac procedures were relatively few in this study. Further, although diagnoses of trisomy 13 and 18 are generally assumed to be fatal within days to weeks after birth, a small but significant subgroup of children with trisomy 13 and 18 are alive over the age of 1 year, and at least some of these children receive substantial inpatient hospital care. Because we are currently unable to identify which children might be long-term survivors, universal application of the term "lethal" to the diagnoses of trisomy 13 and 18 is not appropriate.

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FASTER THAN LIGHT: My father always used to tell me “measure twice, cut once.” I am not remarkably handy around the house, but before I buy windows or flooring or anything else that requires exact measurements, I tend to measure several times before making my purchase. Physicists in Europe must be wishing they had measured a few more times before announcing last year that neutrinos, chargeless and almost massless subatomic particles, travel faster than the speed of light. As reported in The Wall Street Journal (Environment & Science: February 24, 2012), scientists from the European Organization for Nuclear Research now suspect that they may have made a mistake. This turns out to be a huge issue because if neutrinos really can travel faster than the speed of light, then Einstein was wrong and we need to re-think current theories of relativity and gravity and reexamine the laws of particle physics and how the world was formed. When the findings were announced last spring, the scientific world was quite shocked but skeptical since most data had shown that neutrinos were not faster than light. The claim that neutrinos travel faster than light was based on measuring the time that neutrinos sent from a lab in Geneva took to arrive in another lab 450 miles away in Italy. Neutrinos apparently arrived 60 nanoseconds before a light beam would have been expected to arrive. Now scientists are worried that the measurements were off because either an oscillator that synchronizes the clocks in Switzerland and Italy may have been malfunctioning or the fiber-optic cable that transports the Global Positioning System signal to the master clock may not have been working well. This would not be the first time that small problems have led to huge issues. For example, small design flaws in the Hubble space telescope cost hundreds of millions of dollars to fix. The Mars Climate Orbiter was lost because some scientists had used imperial rather than metric units. Still, that a faulty cable may be the reason that fundamental laws of physics were challenged is mind-boggling. The European Organization for Nuclear Research plans to repeat the experiments this spring (with new cables). As for me, I am betting on Einstein.

Noted by WVR, MD
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