Published in final edited form as:

J Perinatol. 2018 August ; 38(8): 1068–1073. doi:10.1038/s41372-018-0136-5.

NICU management and outcomes of infants with Trisomy 21 without major anomalies

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Abstract

Objective: To describe how Trisomy 21 affects neonatal intensive care management and outcomes of full-term infants without congenital anomalies.

Study design: Retrospective cohort of full term infants without anomalies with and without Trisomy 21 admitted to Pediatric NICUs from 2005–2012. We compared diagnoses, management, length of stay and discharge outcomes.

Results: 4,623 infants with Trisomy 21 and 606,770 infants without Trisomy 21 were identified. One-third of infants in the NICU with and without Trisomy 21 were full term without major anomalies. Trisomy 21 infants had more respiratory distress, thrombocytopenia, feeding problems, and pulmonary hypertension. They received respiratory support for a longer period of time and had a longer length of stay.

Conclusion: One-third of infants with Trisomy 21 admitted to the NICU are full term without major anomalies. Common diagnoses and greater respiratory needs place infants with Trisomy 21 at risk for longer length of stay.

Introduction

Trisomy 21 (T21) is the most common chromosomal disorder among live-born infants, occurring in 1 per 700 live births in the United States.¹ Infants with T21 are at increased risk for major congenital anomalies that require management in the neonatal intensive care unit (NICU).^{1,2} Yet nearly 40% of all infants with T21 do not have a major anomaly.³ Even without a major anomaly, infants with T21 are at risk for conditions such as minor cardiac defects, pulmonary hypertension, and laryngomalacia, which cannot always be diagnosed prenatally. These types of diagnoses may result in respiratory and feeding difficulties which require NICU management. It is unknown how many infants with T21 are admitted to the NICU for reasons other than management of major congenital anomalies or prematurity.

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Conflict of Interest

To the best of our knowledge, no conflict of interest, financial or other, exists for any authors. Funding for this study was supported by a Medical College of Wisconsin Presidential Faculty Scholar Award (Lagatta).

Descriptions of the NICU management and survival outcomes of infants with T21 largely focus on those with major congenital anomalies^{3,4,5} or who are very low birth weight.⁶ A more detailed understanding of the medical management of infants with T21 without major anomalies compared to similar infants without T21, and which diagnoses place infants at risk for a longer NICU stay, could help providers set reasonable expectations for families about their infant's hospital course after birth if they do require admission to the NICU. This is especially important since families of infants with T21 report heightened anxiety, feeling overwhelmed and scared surrounding the birth of their child.⁷ Preparing families for a potential NICU course could help mitigate an already stressful pregnancy and postnatal experience.

Our objectives were to use a large multi-center NICU dataset to 1) compare reasons for NICU admission among full term infants without anomalies with and without T21; 2) describe similarities and differences in neonatal medical management between these two groups; and 3) identify which diagnoses are risk factors for a longer NICU length of stay (LOS).

Methods

Data Source

We conducted a retrospective cohort analysis of infants with and without T21 admitted to the NICU from 2005–2012 using the Pediatrix Clinical Data Warehouse (CDW). The CDW collects de-identified electronic medical record data on all infants admitted to 277 academic and private NICUs in 34 states, representing approximately 20% of NICU admissions in the U.S.

All diagnoses generated throughout a patient's NICU hospitalization are recorded in the CDW as entered by the clinician, either by pick list or in free text format. T21 is a discretely coded diagnosis. As described in our prior work,⁸ we manually reviewed all diagnoses and categorized major anomalies similar to reports from the Vermont Oxford Network⁹ and National Institute of Child Health and Development (NICHD) Neonatal Research Network.¹⁰ If an infant had more than one anomaly, each was coded separately. We defined major anomalies as either structural anomalies (i.e. holoprosencephaly) or those for which surgical repair is generally required, even if not always done in the neonatal period. For example, infants with atrio-ventricular canal defects were considered to have major anomalies, although not necessarily requiring repair in the neonatal hospitalization. Isolated cardiac anomalies including atrial septal defect (ASD), ventricular septal defect (VSD) and patent ductus arteriosus (PDA) were not classified as major anomalies since they do not necessarily require NICU admission. The full list of diagnoses considered as major anomalies is listed in Appendix A.

We manually reviewed all diagnoses that were not counted as major anomalies and ranked them by order of prevalence. For subsequent analysis, we recorded all diagnoses present in greater than 1% of infants with T21.

Diagnoses were merged with patient demographic data including gestational age by obstetric estimate, birth weight, maternal age, gender, type of delivery, race and discharge outcome (survived to NICU discharge, transferred or died).

To describe the infant's NICU management, we included the maximal type of respiratory support needed in the NICU: mechanical ventilation (including high frequency oscillatory ventilation and conventional mechanical ventilation), continuous positive airway pressure, high flow nasal cannula, oxyhood or nasal cannula. We also included the total number of days requiring ventilation or non-invasive respiratory support, central line placement, need for vasopressors (dopamine, dobutamine, epinephrine, norepinephrine, or milrinone), surfactant, and inhaled nitric oxide.

Data Analysis

In order to understand reasons for NICU admission, we first compared the distribution of all infants with and without T21 by whether they were preterm (<37 weeks' gestation), had a major anomaly (Appendix A), or neither. We then focused the remainder of our analysis on full term infants (≥ 37 weeks' gestation) without major anomalies with and without T21. Infants with other identified genetic conditions such as trisomy 13, trisomy 18, Turner's syndrome, DiGeorge syndrome, CHARGE or VACTERL sequence were excluded from our analysis.

We compared patient demographics and diagnoses for term infants with and without T21. We also compared NICU medical interventions, mortality, LOS and need for home oxygen or tube feedings at discharge between these two groups. Bivariate analyses were performed by chi squared or Wilcoxon rank sum tests, as appropriate.

Finally, we analyzed which diagnoses were associated with a longer LOS among infants discharged home from the NICU. Infants with and without T21 were assessed in separate models. Diagnoses were entered as covariates into a multivariable generalized linear regression, with standard errors clustered on facility. Because LOS is not normally distributed, the gamma distribution with logit link was applied.¹¹ Odds ratios and 95% confidence intervals (CI) were reported. A p-value of 0.05 was accepted for statistical significance. Stata version 14 was used for all analyses. The study was considered exempt by the Medical College of Wisconsin institutional review board; the Clinical Data Warehouse was approved for research by the Western institutional review board.

Results

Between 2005–2012, 611,393 infants were cared for in 277 Pediatric NICUs; 4623 had T21 and 606,770 infants did not have T21. Infants with T21 were cared for in 248 (78%) Pediatric NICUs.

Figure 1 shows the proportion of infants with and without T21 admitted to a NICU who had major anomalies, were born preterm, or had neither risk factor for NICU admission. Infants with T21 were more likely to have a major congenital anomaly, whereas infants without T21 were more likely to be born preterm (chi squared $p < 0.001$). One-third of infants in the NICU

with T21 were full-term without a major anomaly, which was the same as for infants without T21.

Table 1 shows infant demographic characteristics and diagnoses recorded during NICU admission for the 229,392 full-term infants without major anomalies, comparing infants with and without T21. Infants with T21 were more likely to be born to older mothers, less often Black and more often Hispanic. Other characteristics of infants with and without T21 including gestational age, birth weight, gender, type of delivery and Apgar score at five minutes achieved statistical significance but were clinically similar. The vast majority of NICU admissions for infants with and without T21 occur within the first two days of life, with nearly two-thirds of these admissions occurring on the first day of life for both groups. The most common clinical diagnoses were the same for infants with and without T21; rule out sepsis, hyperbilirubinemia, and respiratory distress were statistically more common in infants with T21 but occurred frequently in both groups. However, infants with T21 had much more frequent diagnoses of thrombocytopenia, PDA, feeding problems, persistent pulmonary hypertension of the newborn (PPHN), VSD and ASD.

Table 2 shows medical interventions and discharge outcomes for full term infants without major anomalies. Infants with T21 were much more likely to receive respiratory support in the NICU, with only 28% remaining in room air compared to 56% of infants without T21. However, this difference was accounted for by non-invasive respiratory support, with no differences in receipt of mechanical ventilation for infants with versus without T21. Vasopressor support and inhaled nitric oxide were more common among infants with T21 compared to infants without T21, but need for these interventions was relatively rare in both groups. Nearly all infants survived to discharge; infants with T21 had significantly higher needs for home oxygen and tube feeds at discharge.

Infants with T21 had a longer LOS in the NICU compared to infants without T21 (median 10 days vs 5 days, $p < 0.001$). Table 3 shows the association between common diagnoses and LOS for infants who survived to NICU discharge, modeled separately for infants with and without T21. Respiratory distress, thrombocytopenia, feeding problems, VSD and sepsis were associated with a longer LOS among both groups. Respiratory distress was associated with a larger increase in LOS for infants with T21 (OR = 1.21, meaning 21% longer LOS) compared to infants without T21 (5% longer), and the same was true for feeding difficulties (66% longer for infants with T21 versus 32% longer for infants without T21). Conversely, PPHN was associated with smaller increase in LOS for infants with T21 (24%) compared to infants without T21 (89%).

Discussion

To our knowledge, this is the first study to report clinical characteristics and outcomes of full-term infants without major anomalies with and without T21 in United States NICUs. Our major observations are:

1. One third of infants with T21 admitted to the NICU are full term without a major anomaly, with conditions that cannot be anticipated prior to delivery.

2. Infants with T21 admitted to the NICU most commonly need non-invasive respiratory support.
3. Several diagnoses, which are more common in infants with T21 than infants without T21 in the NICU, are associated with a longer LOS.

In this study one third of all infants with T21 admitted to the NICU were full term without major anomalies. Although in this study we do not know the number of infants with T21 who received normal newborn care, a recent single-center study in Ireland by Martin et al reported that 87% of all infants with T21 were either directly or subsequently admitted to the NICU prior to discharge home¹². In this analysis, we found similar numbers of full-term infants with T21 with anomalies versus without anomalies. This indicates that despite variation in admission criteria across the 277 U.S. NICUs included in this study, NICU admission for an infant with T21 without anomalies cannot be a rare occurrence. Although ASD, VSD and PDA are considered major anomalies in population-based anomaly registries,³ from a neonatal perspective we intentionally did not categorize ASD, VSD and PDA as major anomalies because they are not always diagnosed prenatally and do not necessarily require NICU admission. Regardless, even these cardiac diagnoses were only present in one-third of infants without other major anomalies. From the perspective of counseling a family prior to delivery, congenital anomalies visible prior to delivery accounted for only 41% of NICU admissions in this study. Most admissions for infants with T21 and no anomaly do occur in the first day of life, with the remaining majority of admissions occurring in the first two days of life. This reinforces the findings by Martin et al¹² and extends them to a multi-center U.S. context, suggesting that prenatal counseling should include information that significant numbers of infants without anomalies may still require NICU care.

Respiratory distress was the main reason for NICU admission in full-term infants with and without T21; more than 75% of infants with T21 admitted to the NICU required some type of respiratory support, which is more than infants without T21. While there are likely variations in admission criteria across hospitals in the U.S. for infants with T21, these data reinforce that the majority of infants with T21 do require medical intervention, rather than observation alone. This is important in the context of parents expecting an infant with T21, who are more likely to undergo substantial prenatal surveillance; they may perceive false reassurance that their infant without prenatal anomalies will have no need for neonatal intervention. It would be helpful to prepare families ahead of time by setting realistic expectations.¹³

As expected, we found that some diagnoses were more common in infants with T21. Three small studies have reported the incidence of pulmonary hypertension in children with T21 to range from 5–34%^{12,14–16}. Among T21 infants without congenital heart disease, the presence of pulmonary hypertension increased LOS, need for mechanical ventilation and need for nitric oxide. Among our subset of infants with T21 admitted to the NICU, we found a 27% prevalence of pulmonary hypertension as recorded by the clinician. It is likely that pulmonary hypertension was overrepresented in this study as it reflects only infants admitted to the NICU rather than the population as a whole. Likewise, most infants with T21 receive screening echocardiograms in the first few days of life to screen for congenital heart disease

but also a time when pulmonary pressures are expected to be high.² However, the fact that pulmonary hypertension was associated with increased LOS suggests that it may be more than selection bias, but a significant contributor to need for NICU management among infants with T21.

Full-term infants without anomalies in the NICU generally experience a short hospital stay, and this is true for infants with and without T21. Several common comorbidities are associated with a greater LOS for both infants with and without T21 including feeding problems, respiratory distress, thrombocytopenia, PPHN, VSD, hypoglycemia and sepsis. In clinical application, these diagnoses cannot be considered “independent” risk factors for longer NICU stay since many of them likely co-occur. Still, a family can be informed that there are several potential issues which each may contribute to the time until they are safely ready for discharge.

From a family perspective, parents expecting an infant with T21 will be worried about the challenges of raising a child with special health care needs.⁷ In that context, it may be helpful to point out that infants with T21 admitted to the NICU have generally the same reasons for admission as term infants without T21, with slightly longer duration of respiratory support needs and LOS. As the first health care providers for these children and their families, neonatologists could use these data as a way to emphasize the similarities between children with and without T21, rather than differences.

The results of this study should be viewed in light of several limitations. We do not have information about the total number of infants with T21 born at all centers who did not require NICU admission, whether the diagnosis of T21 was made prenatally or postnatally, how it was made, or the type of T21 (e.g. full trisomy 21, translocation or mosaicism) for each infant. All clinical diagnoses were recorded by providers and are subject to selection bias; we do not have information about the diagnostic criteria or severity of individual diagnoses. This study does not include information after a child is transferred to a different facility or following NICU discharge. Despite those limitations, this is the first and largest study of clinical risk factors and medical management that affect NICU admission for full term infants with T21 without major anomalies. This fills a gap for counseling families expecting an infant with T21, and allows them to prepare for a broad range of potential neonatal issues.

In conclusion, one third of infants with T21 admitted to the NICU are full term without major anomalies. Compared to term infants without T21 and no major anomaly, infants with T21 have a higher rate of conditions associated with longer NICU length of stay. Clinicians can use this information to provide more detailed counseling to families expecting an infant with T21.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Source of funding: Dr. Lagatta was supported in part by a Presidential Faculty Scholar Award from the Medical College of Wisconsin.

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Figure 1. NICU admissions of infants with and without T21 by presence of major anomaly and prematurity.

Figure 1 shows infants with and without T21 admitted to 277 Pediatrix NICUs between 2005–2012, categorized by whether the infant had a major anomaly, was born preterm, or neither. Abbreviations: T21, Trisomy 21. Major anomaly was defined according to those listed in Appendix A. Prematurity was defined as <37° weeks' gestation.

Table 1.

Demographics and common NICU diagnoses among full term infants without major anomalies with and without T21.

	T21 (n=1686)	No T21 (227,706)	p-value
DEMOGRAPHICS			
Gestational age, weeks, median (IQR)	38 (37–39)	39 (38–40)	<0.001
Birth weight, grams, median (IQR)	3103 (2760–3448)	3310 (2957–3675)	<0.001
Maternal age, years, median (IQR)	34 (27–39)	27 (22–32)	<0.001
Male gender	910 (54%)	132,069 (58%)	0.001
Cesarean section delivery	725 (43%)	102,468 (45%)	0.081
Race/ethnic group			
White	809 (48%)	133,299 (48%)	<0.001
Black	152 (9%)	41,656 (15%)	
Hispanic	523 (31%)	72,204 (26%)	
Other	202 (12%)	30,547 (11%)	
Outborn delivery	337 (20%)	44,433 (16%)	<0.001
Apgar score at 5 minutes	9 (8–9)	9 (8–9)	<0.001
COMMON DIAGNOSES			
Rule out sepsis	1346 (80%)	172,971 (77%)	<0.001
Hyperbilirubinemia	1098 (65%)	94,861 (42%)	<0.001
Respiratory distress	973 (58%)	113,268 (50%)	<0.001
Thrombocytopenia	641 (38%)	10,516 (5%)	<0.001
PDA	618 (37%)	6644 (3%)	<0.001
Feeding problems	573 (34%)	34,715 (15%)	<0.001
PPHN	458 (27%)	6783 (3%)	<0.001
VSD	419 (25%)	3208 (1.4%)	<0.001
ASD	257 (15%)	1896 (0.8%)	<0.001
Hypoglycemia	257 (15%)	29,403 (13%)	0.004
Polycythemia	199 (12%)	1,962 (0.8%)	<0.001
Sepsis	179 (11%)	32,383 (14%)	<0.001

Data are presented as n (%) unless indicated otherwise.

Abbreviations: NICU, neonatal intensive care unit; T21, Trisomy 21; IQR, inter-quartile range; PDA, patent ductus arteriosus; PPHN, persistent pulmonary hypertension of the newborn; VSD, ventricular septal defect; ASD, atrial septal defect.

Table 2.

NICU interventions for full term infants without major anomalies with and without T21.

	T21 (n=1686)	No T21 (n=227,706)	p-value
Maximal respiratory support			
Mechanical ventilation	163 (9.7%)	20,507 (9%)	0.34
Continuous positive airway pressure	118 (7%)	18,861 (8.3%)	0.05
High flow nasal cannula	359 (21.3%)	23,960 (10.5%)	<0.001
Oxyhood or nasal cannula	575 (34.1%)	35,539 (15.6%)	<0.001
None	471 (27.9%)	126,352 (55.5%)	<0.001
Total respiratory support days	5 (3–11)	2 (1–4)	<0.001
Other NICU interventions			
Central line	376 (22%)	32,945 (14%)	<0.001
Vasopressor	77 (5%)	5,902 (3%)	<0.001
Surfactant	44 (3%)	11,216 (5%)	<0.001
Inhaled nitric oxide	59 (4%)	2,373 (1%)	<0.001
Discharge outcome			
Survived	1,511 (89.6%)	191,686 (84.2%)	<0.001
Transferred	165 (9.8%)	35,271 (15.3%)	<0.001
Died	10 (0.6%)	749 (0.3%)	<0.001
Length of stay, survivors, median (IQR)	10 (6–17)	5 (3–7)	<0.001
Home discharge supports, survivors			
Home oxygen	126 (8.3%)	1288 (0.7%)	<0.001
Tube feeds (Gastrostomy or nasogastric)	80 (5.2%)	692 (0.4%)	<0.001

Data are presented as n (%) unless indicated otherwise.

Total respiratory support days = the number of days requiring any type of respiratory support other than room air. Central line = peripherally inserted central catheter, umbilical catheter, or surgically placed central line. Vasopressor = dopamine, dobutamine, epinephrine, norepinephrine, milrinone.

Abbreviations: NICU, neonatal intensive care unit; T21, Trisomy 21; IQR, inter-quartile range.

Table 3.

Diagnoses associated with longer NICU length of stay among surviving full term infants without major anomalies with and without T21.

DIAGNOSIS	T21 (n=1,511)			No T21 (n=191,686)		
	Odds Ratio	95% CI	p-value	Odds Ratio	95% CI	p-value
Rule out sepsis	1.14	1.00, 1.30	0.007	0.95	0.88, 1.03	0.2
Hyperbilirubinemia	1.00	0.90, 1.10	0.9	1.05	1.01, 1.01	0.01
Respiratory distress	1.21	1.10, 1.30	<0.001	1.05	1.01, 1.09	0.011
Thrombocytopenia	1.30	1.20, 1.40	<0.001	1.43	1.38, 1.48	<0.001
PDA	1.05	0.96, 1.15	0.27	1.19	1.15, 1.23	<0.001
Feeding problems	1.66	1.48, 1.86	<0.001	1.32	1.22, 1.42	<0.001
PPHN	1.24	1.12, 1.37	<0.001	1.89	1.80, 1.99	<0.001
VSD	1.24	1.13, 1.36	<0.001	1.22	1.16, 1.27	<0.001
ASD	1.09	0.98, 1.20	0.08	1.37	1.27, 1.48	<0.001
Hypoglycemia	1.14	1.04, 1.26	0.004	1.04	1.00, 1.07	0.02
Polycythemia	1.07	0.95, 1.21	0.2	1.05	1.00, 1.11	0.04
Sepsis	1.27	1.12, 1.44	<0.001	1.26	1.17, 1.36	<0.001

Table 3 presents results of regression models for associations between common diagnoses and longer length of stay among surviving infants discharged home from the NICU, performed separately for infants with and without T21.

Data are presented as odds ratio and 95% confidence interval following a generalized linear model with gamma distribution and logit link, with standard errors clustered on facility. Models are also adjusted for birthweight, sex, multiple gestations, race and maternal age.

Abbreviations: T21, Trisomy 21; NICU, neonatal intensive care unit; CI, confidence interval; PDA, patent ductus arteriosus; PPHN, persistent pulmonary hypertension of the newborn; VSD, ventricular septal defect; ASD, atrial septal defect.