Medication Utilization in Children Born Preterm in the First Two Years of Life

Jonathan C Levin, MD MBI[1,2,3], **Andrew L Beam, PhD**[4], **Kathe P Fox, PhD**[5], **Kenneth D. Mandl, MD MPH**[1,3,5]

[1]Computational Health Informatics Program, Boston Children's Hospital, Boston MA

[2]Divisions of Newborn and Pulmonary Medicine, Boston Children's Hospital, Boston MA

[3]Department of Pediatrics, Harvard Medical School, Boston MA

[4]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston MA

[5]Department of Biomedical Informatics, Harvard Medical School, Boston, MA

Abstract

Objective: To compare medications dispensed during the first two years in children born preterm and full-term.

Study Design: Retrospective analysis of claims data from a commercial national managed care plan 2008–2019. 329 855 beneficiaries were enrolled from birth through two years, of which 25 408 (7.7%) were preterm (<37 weeks). Filled prescription claims and paid amount over two years were identified.

Results: In preterm children, the number of filled prescriptions was 1.4 times and cost was 3.8 times that of full-term children. Number and cost of medications were inversely related to gestational age. Differences peak at 4–9 months and resolve by 19 months after discharge. Palivizumab, ranitidine, albuterol, lansoprazole, budesonide, and prednisolone had the greatest differences in utilization.

Conclusion: Prescription medication utilization among preterm children under two is driven by palivizumab, anti-reflux, and respiratory medications, despite little evidence regarding efficacy for many medications, and concern for harm with certain classes.

Corresponding Author: Jonathan Levin, MD MBI, Boston Children's Hospital, 300 Longwood Ave Hunnewell 4, Boston, MA 02115, jonathan.levin@childrens.harvard.edu, 617-355-1900.

Introduction

Over 380 000 newborns in the United States, or nearly one in ten births, are preterm at less than 37 weeks gestation.[1] Healthcare utilization in this population in the first two years of life is high, with increased hospitalizations, visits, and medication usage.[2–4]

Though it is known that preterm infants are exposed to a high number of medications during their admission to the neonatal intensive care unit (NICU), there are few reports characterizing patterns in dispensed medications after discharge from the NICU.[5] A study on a regional cohort from 1999–2001 suggested high rates of dispensed medications in the first year of life (mean 5.5 per year). Respiratory medication (49%) and anti-reflux medication (37%) are frequently used.[3,6] Since that time, new evidence has emerged raising safety concerns for anti-reflux medications, with limited evidence of efficacy in infants under a year of age.[7,8] Further, recognition of carcinogenic impurities has resulted in multiple medications being taken off market.[9–13]

Other studies suggest frequent use of asthma medications in childhood among former preterm infants, despite little data regarding their efficacy and safety (particularly for inhaled corticosteroids).[14–16] Among former preterm infants <29 weeks gestation with respiratory disease, patients from the Premature Respiratory Outcome Program cohort had increased exposure to bronchodilators and inhaled corticosteroids over the course of the first year of life, with a majority of patients receiving a prescription for at least one respiratory medication.[17,18]

Longitudinal national-level claims data offer a unique opportunity to explore neonatal outcomes, including recent trends of prescription medication use among preterm infants, especially as compared to a full-term population. We sought to compare prescription frequency and cost in cohorts of children born preterm and full-term over the first two years of life and identify the specific medications that account for the preponderance of the difference between these groups.

Subjects and Methods

Data Source

The population is a retrospective cohort of beneficiaries from a large private, national managed care plan with claims data from 2008–2019. We included 329 855 beneficiaries who were enrolled from birth through two years of age and had both medical and pharmacy benefits. We identified 25 408 (7.7%) preterm infants based on the presence of an International Classification of Diseases (ICD) code for prematurity at any encounter during enrollment, using ICD codes for prematurity with gestational age (GA) less than 37 weeks and/or birth weight < 1500g (ICD-9 code category 765 and ICD-10 code category P07); the remainder 304 447 were otherwise categorized as full-term. Gestational age was defined by ICD code, where available. The dataset includes demographics, enrollment and claims. These data have previously been used for many studies, including costs of prematurity, genetic and environmental contributions to phenotypes among twins and sibling pairs, 17-

OHP use to prevent preterm birth, and pediatric pulmonary hypertension phenotypes, among others.[4,19–21]

Medication Claims

We identified national drug codes and the amount paid over the entire time period for unique pharmaceutical claims for medications dispensed to members of the cohort. Cost was defined as the sum of amount paid by the insurer and member out of pocket cost. Medications were grouped by the first word of the generic name and route of administration.

The rate ratio of filled prescriptions (total claims and unique medications) as well as the cost ratio in children born preterm compared those born full-term over the 2 year follow-up period were calculated. Subgroup analysis was conducted on children born early preterm (32 completed weeks gestation) and those born moderate-late preterm (33–36 completed weeks gestation). A post-hoc analysis excluded palivizumab, as this was a large driver of cost differences but is clinically indicated for much of the early preterm population.

In a subanalysis of the first 12 months after newborn discharge, time of newborn discharge was determined as the last discharge date on contiguous inpatient encounters (encounters for which a one's discharge date matches another's admission date, to account for patient transfers). This was done to account for time duration in the hospital when newborns are not receiving outpatient medications. Outpatient medications dispensed 7 days prior to hospital discharge were included in analysis.

We then performed an analysis of individual medications and calculated risk difference, risk ratio, cost difference and cost ratio between each subgroup and full-term infants. We identified ten medications with the greatest risk difference per person between groups, and for each medication, calculated the duration supplied (which is available from each pharmaceutical claim) over 2 years per member, among members prescribed that medication.

Statistical analysis

Analyses were performed with Microsoft SQL Server (2018, version 17.9) and R version 3.5.2 (2018), using software packages (tidyverse version 1.2.1, fmsb version 0.6.3). Comparisons for each preterm group (early preterm and moderate-late preterm) were made to the reference group of full-term infants. Formal power calculations were not performed given the large sample sizes. Two-sided Poisson tests were used to compare incidence rates of total dispensed prescriptions and unique dispensed medications between each group. For cost data, given the large sample size, two-sided t-tests were used to compare medication cost per member for each group. A linear regression model was used to calculate the effect of gestational age on dispensed prescriptions and cost per member. For the medications with the greatest risk difference per person between groups, duration of supply per member was compared between each group using two-sided t-tests. For all statistical tests, $p < 0.05$ was considered significant. No corrections for multiple testing were employed.

IRB

The Boston Children's Hospital Institutional Review Board approved the study, granting a waiver of consent.

Data and Code Availability

Code used to generate the results is available by request to the corresponding author; however, per terms of the health plan supplying the data, and because of the risk of reidentification, the underlying patient data are not able to be shared.

Results

Among the 329 855 individuals enrolled from birth through 2 years of age with the pharmacy benefit, 25 408 (7.7%) were identified as preterm < 37 weeks and 304 447 were otherwise categorized as full-term. 19,555 (77%) of preterm infants had gestational age ICD codes; the remainder did not have an ICD code identifying birth GA, but had other codes indicating prematurity (birthweight or unspecified GA, see supplement). Of these, 3 592 (18%) were born early preterm and 15 963 (82%) born moderate-late preterm. Mean GA for all preterm infants was 33.9 weeks (range 22–36 weeks completed). 54% of early preterm infants and 53% of moderate-late preterm infants were male versus 51% of full-term infants (both p<0.001 by chi squared).

There were 209 469 filled prescriptions among children born preterm (8.2 per patient, $1888 per patient over two years) and 1 863 159 total filled prescriptions among children born full-term (6.1 per patient, $500 per patient over two years). Children born preterm filled prescriptions at a rate of 1.3 times (95% CI 1.3–1.4; p < 0.0001) and at a cost ratio of 3.6 times (95% CI 3.3–3.9; p < 0.0001) that of those born full-term. Children born early preterm filled prescriptions at a rate of 1.8 times (95% CI 1.8–1.9, p < 0.0001) at a cost ratio of 11.5 times (95% CI 10.3–12.7, p<0.001) that of those born full-term. Children born moderate-late preterm filled prescriptions at a rate of 1.2 times (95% CI 1.2–1.2, p < 0.0001) and cost ratio was 1.7 times (95% CI 1.5–1.9, p < 0.0001) that of those born full-term. Unique medication claims were also higher in children born preterm. Costs remained higher for children born preterm in a subanalysis excluding palivizumab (Table 1). Rate and cost ratios of filled prescriptions were also higher in each group in a subanalysis of 12 months after newborn hospitalization discharge (Supplement).

Total utilization and cost were inversely correlated to birth gestational age using a linear model, though highly variable. There were 0.06 fewer prescriptions for each additional week GA (p < 0.0001, R-squared = 0.03). Cost was $574 less over 2 years for each additional week GA (p < 0.0001, R-squared = 0.08). Cost was notably higher among children born <29 weeks gestation. Utilization and costs peaked between 4–9 months after newborn hospitalization discharge. Differences in utilization and cost resolve by 19 months after discharge (Figure 1).

The most frequent medications in children born preterm, by total number of prescriptions, were amoxicillin, albuterol, ranitidine, cefdinir, and palivizumab, and prednisolone. For the entire cohort (preterm and full-term), the most frequent medications were amoxicillin,

cefdinir, albuterol, azithromycin, nystatin, and prednisolone. Medications with the greatest frequency difference in children born preterm and those full-term were palivizumab, ranitidine, albuterol, lansoprazole, budesonide, and prednisolone; palivizumab was by far the greatest contributor in cost difference (Table 2 and 3). Among the ten medications having greatest differential use between children born early preterm and those full-term, duration of supply was longer in early preterm infants for albuterol, ranitidine, budesonide, prednisolone, lansoprazole, and fluticasone, and was shorter for spironolactone (Figure 2).

Discussion

There is a substantial medication burden among children born preterm compared with those born full-term in the first two years of life, especially at lower birth gestational ages. Aside from palivizumab, which has a specific indication for children born preterm, medications with the greatest difference in utilization in children preterm versus full-term infants include anti-reflux medications and respiratory medications. In addition, many of these medications were prescribed for longer durations in children born preterm (other than spironolactone, which is likely being used for other chronic conditions, e.g. cardiac disease, in full-term children). The greater frequency and duration of prescriptions suggest considerably higher medication exposure, even after NICU discharge, in preterm children.

There were differences in utilization among both the early preterm) and moderate-late preterm groups. Though the magnitude of difference compared to full-term was less in the moderate-late preterm group, the total burden in this population is greater due to the greater numbers of moderate-late preterm births; this is a relatively understudied population compared to early-preterm infants.[22]

These data offer a unique opportunity to explore neonatal outcomes, which have traditionally been reported in prospective cohorts followed over time, or using individual trial data.[23–27] While these longitudinal cohorts have been extremely valuable to help define specific outcomes of prematurity, they are limited at (1) capturing comprehensive, 'real-world' utilization and costs data over multiple sites, including private primary care practices, community hospitals, and tertiary care centers; (2) representing a broad population of former preterm infants, including those born moderately or late preterm; and (3) identifying trends in larger populations, given cohort attrition and the resources required to follow over long periods of time.

Few other studies have focused on medication use after NICU discharge. The rates of medication use we find is similar to those from reports of smaller, regional cohorts using claims data from 10–20 years ago. These medication use patterns persist despite new evidence that has emerged concerning the safety and efficacy of anti-reflux medications, in particular.[3] Our data also matches previous data regarding increasing rates of respiratory medication use (bronchodilators and inhaled corticosteroids) in the first year, though total usage was less than previous reports, possibly diluted due to our inclusion of infants born at later gestational ages.[17]

The high utilization of respiratory medications and anti-reflux medications is notable given that in former preterm infants, there is little evidence for efficacy of these medications, with minimal safety data and at times potential for harm.[18] In general, only 35% of all medications used in the NICU are Federal Drug Administration approved in infants.[28] Respiratory medications are frequently prescribed off FDA label to young children.[29] With anti-reflux medications, there is emerging evidence of adverse effects in preterm infants, including necrotizing enterocolitis, late-onset infections, alteration of the intestinal microbiome, fracture risk, and death.[6,11,30] This report highlights the need for increased surveillance of their use in the community after NICU discharge.

Strengths of this study include the size of this national-scale cohort, much greater than could be followed using prospective cohort studies. We also were able to utilize a control full-term population, and able to focus on differences in utilization between these groups. The study also measures closer to true utilization of medications, given that claims only represent filled prescriptions, especially as high rates of medication non-adherence have been reported in this population.[31]

Limitations include the use of medical claims to identify preterm infants and identify outcomes. Primary purpose of medical claims is billing rather than research; thus there may be biases in recorded codes and encounters. The premature rate of 8% in the database is slightly less than the nationally reported rate of 10%; this may be due to undercoding.[1] However, if some preterm infants were misclassified as full-term, that would only stand to strengthen the differences found in this study. Additionally, while the cohort is nationally representative, it represents private commercial health benefits; there may be different findings in publicly insured patients. Finally, medications not covered by insurance, such as those paid for directly by the patient, over the counter medications, and those covered by secondary insurance are not available.

This study demonstrates that prescription medication utilization is notably higher among children born preterm compared to those born full-term in the first two years of life, especially at lower gestational ages. Aside from palivizumab, medications with the greatest difference in utilization between children born preterm (in both early preterm and moderate-late groups) include anti-reflux and respiratory medications. Further work using longitudinal medical and pharmaceutical claims data may give important clues about the effectiveness and impact of medication usage in former preterm infants, especially when randomized clinical trials are difficult to complete due to resources required, cohort identification, and ethical considerations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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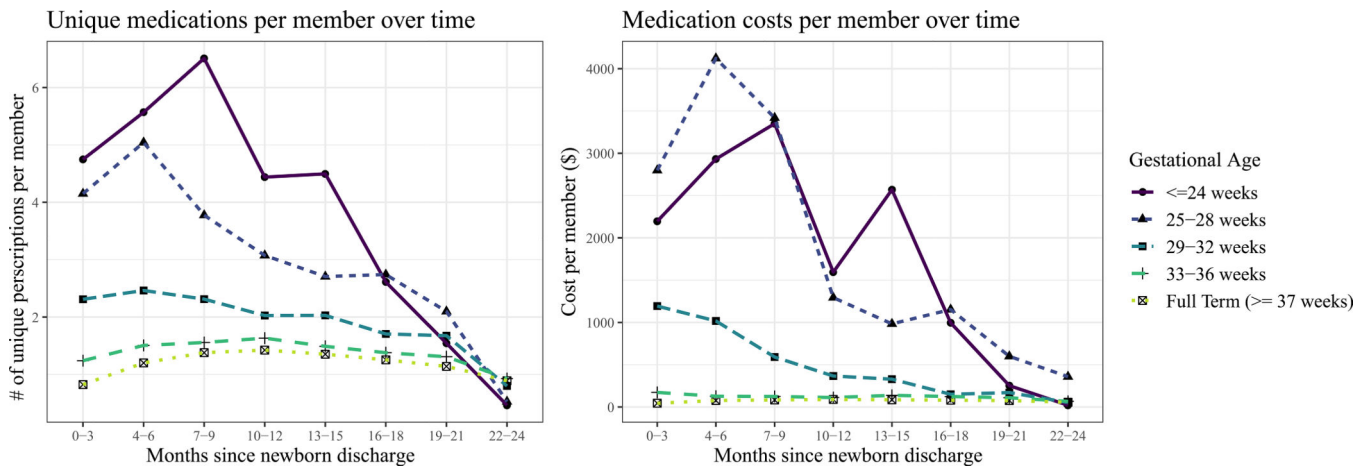
Figure 1. Unique medications prescribed and costs by gestational since neonatal discharge

Medications and cost over time since newborn hospital discharge, stratified by Gestational Age. Costs were defined as the sum of amount paid by the insurer and member out of pocket costs.
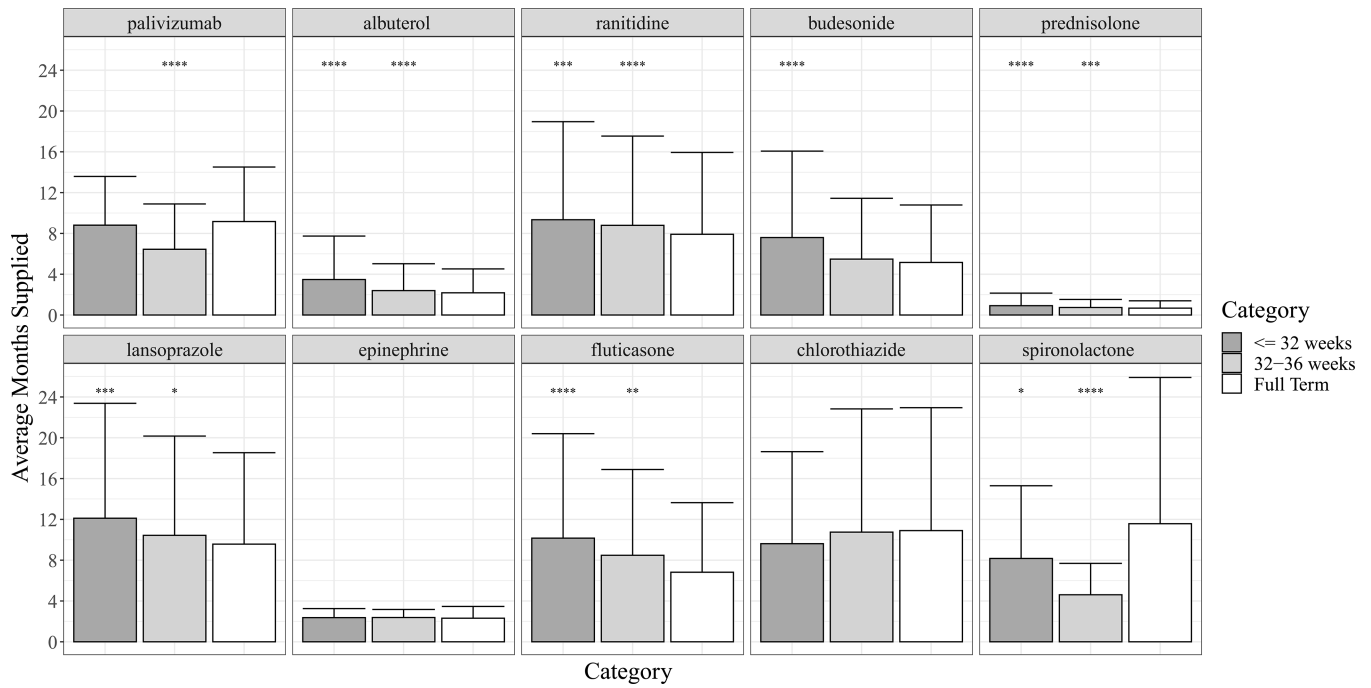
Figure 2. Duration of Supply among medications with greatest difference in prescribing frequency

Medications selected are those with the ten greatest risk difference between early preterm (32 weeks) and full-term population selected for visualization. Height of bars represent mean. Error bars represent standard error. * = p < 0.05, ** = p   0.01, *** = p   0.001 compared to full-term group by two-sided t test. GA = Gestational Age

Table 1.

Medication Utilization and Cost Differences over First Two Years

	Early Preterm 32 Completed Weeks (N=3 592)	Moderate-Late Preterm 33–36 Completed Weeks (N=15 963)	Full-Term (ref) (N=304 447)
Male	1 936 (54%) [*]	8 477 (53%) [*]	156 085 (51%)
Mean Completed Weeks of Gestation (Range)		33.9 (22–36)	N/A
Filled Prescriptions per patient	11.3	7.3	6.1
Rate Ratio Of Filled Prescriptions (95% CI)	1.8 (1.8–1.9) [*]	1.2 (1.2–1.2) [*]	
Cost per Patient	$6242	$871	$500
Cost Ratio per Patient(95% CI)	11.5 (10.3–12.7) [*]	1.7 (1.5–1.9) [*]	
Unique Medications per patient	4.5	3.6	3.2
Rate Ratio Of Unique Medications (95% CI)	1.4 (1.4–1.4) [*]	1.1 (1.1–1.1) [*]	
Filled Prescriptions per Patient excluding palivizumab	10.3	7.2	6.1
Rate Ratio excluding palivizumab (95% CI)	1.7 (1.7–1.7) [*]	1.2 (1.2–1.2) [*]	
Cost per Patient excluding palivizumab	$1133	$623	$464
Cost Ratio per Patient excluding palivizumab (95% CI)	2.3 (1.9–2.7) [*]	1.3 (1.1–1.5) [*]	

[*] $p < 0.001$ compared to Full-Term by Chi-squared (gender), Poisson test (Rate Ratio), or t test (Cost ratio). Rate and Cost ratios compared to full-term (reference).

Table 2.

Top Medications by Risk Difference, Early Preterm (32 completed weeks) vs Full-Term

Medication	Risk Difference	RR (95% CI)	Cost Difference per patient ($)	Cost Ratio per patient
Palivizumab IM	0.26	149 (135–164)	5,073	143
Albuterol INH	0.13	1.9 (1.8–2.0)	23.7	3.0
Ranitidine PO	0.12	2.9 (2.7–3.1)	12.2	3.1
Budesonide INH	0.072	2.8 (2.5–3.1)	137	4.3
Prednisolone PO	0.072	1.5 (1.4–1.6)	1.4	1.6
Lansoprazole PO	0.065	4.0 (3.6–4.5)	52	3.5
Epinephrine IM	0.046	163 (126–211)	0.14	13.1
Fluticasone INH	0.032	4.1 (3.5–4.8)	34.4	6.4
Chlorothiazide PO	0.032	129 (97–172)	3.5	117
Spironolactone PO	0.025	67 (51–87)	1.7	35.6

IM = Intramuscular; INH = Inhaled; PO = oral.

Table 3.

Top Medications by Risk Difference, Moderate-Late Preterm (33–36 completed weeks) vs Full-Term

Medication	Risk Difference	RR (95% CI)	Cost Difference per patient ($)	Cost Ratio per patient
Ranitidine PO	0.049	1.8 (1.7–1.9)	3.7	1.6
Albuterol INH	0.038	1.2 (1.2–1.3)	4.1	1.3
Lansoprazole PO	0.022	2.0 (1.9–2.2)	23	2.1
Prednisolone PO	0.020	1.1 (1.1–1.2)	0.52	1.2
Palivizumab IM	0.018	11.1 (9.6–12.7)	212	6.9
Budesonide INH	0.015	1.4 (1.3–1.5)	23.4	1.6
Nystatin TOP	0.012	1.1 (1.0–1.1)	0.86	1.1
Cefdinir PO	0.0093	1.0 (1.0–1.1)	0.61	1.0
Oseltamivir PO	0.0089	1.3 (1.2–1.3)	1.8	1.3
Ondansetron PO	0.0078	1.2 (1.1–1.3)	−0.11	0.94

IM = Intramuscular; INH = Inhaled; PO = oral; TOP = topical.