A prospective cohort study was performed in preterm infants less than 32 weeks gestation at birth who were treated with dexamethasone for developing or established bronchopulmonary dysplasia (BPD). Respiratory phenotype (Respiratory Severity Score (RSS)), serum, and urine metabolomics were assessed before and after treatment. Ten infants provided nine matched serum and nine matched urine samples. There was a significant decrease in RSS with steroid treatment. Serum gluconic acid had the largest median fold change (140 times decreased, \( P = 0.008 \)). In metabolite set enrichment analysis, in both serum and urine, the urea cycle, ammonia recycling, and malate-aspartate shuttle pathways were most significantly enriched when comparing pretreatment and post-treatment (\( P \) value < 0.05). In regression analyses, 6 serum and 28 urine metabolites were significantly associated with change in RSS. Urine gluconic acid lactone was the most significantly correlated with clinical response (correlational coefficient 0.915). Pharmacometabolomic discovery of drug response biomarkers in preterm infants may allow precision therapeutics in BPD treatment.

Bronchopulmonary dysplasia (BPD) is a lung disease that results from the combination of preterm birth, ventilator-associated lung injury, inflammation, and maladaptive lung growth. BPD is a common diagnosis in the neonatal intensive care unit (NICU), but there are no US Food and Drug Administration (FDA)- approved therapies for management. One class of drugs commonly used to prevent severe BPD, or to treat established BPD, are corticosteroids. Use of this drug class in neonates and infants with BPD is challenging because of variability in clinical wanted effects and an inability to target infants who are likely “responders.” Neonatologists lack an early biomarker of likely drug effect and cannot personalize therapy to improve outcomes.

Pharmacometabolomics is a novel and powerful tool to help understand variability in drug response. A patient metabolotype, or the full complement of circulating molecules in the plasma or urine, can be defined pretreatment and post-treatment with a drug. Either baseline metabolotype or change in metabolotype, in conjunction with close measurement of drug response, can inform treatment outcomes.
Metabotype at baseline, and the discovery of signature metabotype changes with certain drug exposures, can elucidate the mechanisms of variation in drug response. For example, if a metabolic signature of responders vs. nonresponders was available before treatment or early in the drug treatment course, then infants in the nonresponder group could receive alternate therapies empirically, or at least be spared the full 7–10 day course of steroids, which have been associated with adverse outcomes.\textsuperscript{2,3}

Given the variability in steroid response observed in clinical practice, our goal is to perform a prospective cohort steroid pharmacometabolomic study nested in routine clinical care of preterm infants with evolving or established BPD. During this exploratory project, we aim to identify metabolic changes that correlate with drug response and drug failure. Because neonatal metabolomics is an emerging field, our group aims to discover treatment response biomarkers and generate hypotheses for future research.

**METHODS**

**Subjects and study design**

This prospective pilot cohort study was reviewed and approved by the Children’s Mercy Hospital institutional review board prior to patient enrollment. Parental consent was obtained in accordance with institutional review board regulations. Starting in October 2016, all preterm infants less than 32 weeks gestation at birth and treated with systemic dexamethasone per clinical care were eligible for enrollment. Demographic data and clinical data were abstracted from the clinical chart and by speaking with bedside clinicians in realtime. For this analysis, we only used data from the first course of systemic dexamethasone for each child.

In order to measure the clinical outcome, we measured short-term phenotypic response to systemic corticosteroids. The Respiratory Severity Score (RSS) was calculated before treatment (baseline) and on day 7 of treatment (drug response). In order to account for intraindividual variability, the average RSS for a 24-hour period was collected. The RSS is a quantitative description of the severity of lung disease while on mechanical or noninvasive ventilation. Lower values of the RSS indicates better pulmonary function. RSS is calculated as the mean airway pressure $\times$ fraction of inspired oxygen (FiO$_2$) (ranging from 21–100%). After starting treatment with dexamethasone, clinicians want the RSS to go down as pulmonary mechanics and gas exchange improve.

Blood and urine samples were collected two times, once in the 24 hours prior to starting systemic dexamethasone and once at days 3–6 after starting systemic dexamethasone. Both matrices were studied because the urine can be collected noninvasively with a cotton ball, whereas the serum may be a better reflection of pulmonary changes. The timing of post-treatment blood and urine sample was dictated by the infant having blood drawn for clinical laboratories within the target window. Samples were collected in the NICU and then either briefly refrigerated or immediately processed. Urine and serum were aliquoted and stored at –80°C until metabolomic assay.

**Untargeted metabolomic assessment**

Serum and urine samples were submitted for an untargeted metabolomic analysis through the National Institutes of Health (NIH)-funded West Coast Metabolomics Center in Davis, California. For analysis of serum and urine metabolites, metabolite levels were determined using an Agilent 7890A gas chromatograph coupled to a Leco Pegasus IV time-of-flight mass spectrometer, as previously described.\textsuperscript{4} Acquired spectra were further processed using the 130 BinBase database,\textsuperscript{4,5} including metabolite annotations by retention index and mass spectra matching. Data, reported as quantitative ion peak heights, were normalized by the sum intensity of all annotated metabolites across the entire study and used for further statistical analysis.

**Statistical analysis**

The change in RSS, the clinical outcome, was assessed before and after treatment using the Wilcoxon signed rank test. In order to test for an association between baseline metabolite level and change in RSS, we performed regression analysis.

| Infant | GA (weeks) | BW (kg) | Race | DOL steroid | Pre-RSS | Post-RSS | Change in RSS | Sample collection | Serum analysis | Urine analysis |
|--------|------------|---------|------|------------|---------|----------|---------------|-------------------|----------------|---------------|
| 1      | 25 1/7     | 0.480   | WH   | AA         | 138     | 11.02    | 0.50 (nasal cannula) | −10.52          | 7.3            | x             | x             |
| 2      | 25 0/7     | 0.420   | AA   | 36         | 4.65    | 2.63     | −2.02         | 3.50             | x             | x             |
| 3      | 23 4/7     | 0.625   | HIS  | 36         | 9.75    | 3.87     | −5.88         | 5.33             | x             | x             |
| 4      | 23 4/7     | 0.595   | HIS  | 27         | 8.03    | 2.90     | −5.13         | 4.38             | x             | x             |
| 5      | 25 2/7     | 0.725   | HIS  | 36         | 3.96    | 2.31     | −1.65         | 5.63             | x             | x             |
| 6      | 24 6/7     | 0.700   | HIS  | 36         | 4.40    | 2.43     | −1.97         | 6.58             | x             | x             |
| 7      | 28 6/7     | 1.530   | WH   | 26         | 7.80    | 2.99     | −4.81         | 4.42             | x             | −             |
| 8      | 24 4/7     | 0.370   | AA   | 127        | 8.78    | 8.16     | −0.6          | 5.54             | x             | x             |
| 9      | 25 5/7     | 0.850   | WH   | 33         | 5.16    | 2.57     | −2.59         | 6.50             | −             | x             |
| 10     | 26 4/7     | 0.770   | WH   | 111        | 2.34    | 0.50     | −1.84         | 3.50             | x             | x             |
| Median | 25 0/7     | 0.663   | —    | 36         | 6.48    | 2.6      | −2.3          | 5.44             | −             | −             |

**Table 1. Demographic and respiratory data**

AA, African American; BW, birthweight; DOL steroid, day of life (age) when infant started steroids; GA, gestational age; HIS, Hispanic; IQR, interquartile range; RSS, Respiratory Severity Score; Sample collection, number of days from steroid start to post-treatment metabolomic sample collection; WH, white.
analysis. The differences in the metabolites assayed before and after treatment were assessed using the Wilcoxon signed rank test for each metabolite followed by multiple testing adjustments using Benjamini and Hochberg’s false discovery rate method.

Each metabolite change was assessed from pretreatment to post-treatment using the Wilcoxon signed rank test and then they were sorted by the order of significance ($P$ value). Then, Metabolite Set Enrichment Analysis (MSEA) was completed, as previously described $^6,7$ using MetaboAnalyst version 4.0. MSEA is a method of identifying biologically meaningful patterns or the metabolic pathways that are significantly enriched in quantitative metabolomic data. The MSEA as implemented in the MetaboAnalyst version 4.0 $^8$ uses the hypergeometric distribution based test followed by multiple test adjustments to evaluate whether a particular metabolite set is represented more than expected by chance within the given compound list.

Next, the association of change in metabolites with the change in the RSS scores before and after treatment was investigated using linear regression and correlation analyses. Prior to fitting the linear regression models, the association

Figure 1. Change in phenotype and example metabolite with dexamethasone therapy. Boxplots displaying (a) change in Respiratory Severity Score and (b) change in trans-4-hydroxyproline, an example metabolite that nearly universally decreased with steroid treatment.
of RSS with the birth weight, gender, race, mode of delivery, and antenatal steroids were examined. None of the variables were found to be associated with the RSS for both serum and urine, so they were not included in the regression model. Finally, for the exploratory analysis, the subjects were grouped into good, moderate, and poor responders' categories based on a decrease in RSS score. The top three subjects that had maximum decrease in RSS score were categorized as "good" responders, the three subjects having the least decrease in RSS were categorized as "poor" responders, and the remaining as "moderate" responders. The differences in the changes in metabolites among the three groups were assessed using the Kruskal–Wallis test. The tests were considered significant if the $P$ value was <0.05.

The analyses were carried out separately for the serum and urine. All the analyses were performed using Statistical Software R (R Foundation for Statistical Computing, Vienna, Austria) and MetaboAnalyst version 4.0.

**RESULTS**

Ten infants (median birthweight 663 g; median gestational age 25 0/7 weeks) provided nine matched pre-steroid and post-steroid treatment serum samples and nine matched pre-steroid and post-steroid treatment urine samples for analysis. Infant demographic and clinical phenotypic response data are provided in Table 1. All infants were treated with a protocolized dexamethasone wean over 7–10 days

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**Table 2. Metabolite changes with dexamethasone therapy**

| Metabolites       | Median (pre) | Median (post) | Fold change | Direction | $P$ value$^a$ |
|-------------------|--------------|---------------|-------------|-----------|--------------|
| **Serum**         |              |               |             |           |              |
| Oxalic acid       | 10,808       | 15,403        | 1.425148    | Up        | 0.0039       |
| Lactic acid       | 41,371       | 81,823        | 1.977786    | Up        | 0.0039       |
| Malic acid        | 405          | 837           | 2.066667    | Up        | 0.0078       |
| Gluconic acid$^b$| 115,513      | 826           | 0.007151    | Down      | 0.0078       |
| Caprylic acid     | 902          | 4,800         | 5.321508    | Up        | 0.0078       |
| Alpha-ketoglutarate| 669       | 958           | 1.431988    | Up        | 0.0117       |
| Saccharic acid$^b$| 8,474        | 868           | 0.102431    | Down      | 0.0273       |
| Cholesterol       | 1,581        | 2,221         | 1.404807    | Up        | 0.0273       |
| Arachidic acid    | 2,671        | 3,980         | 1.490079    | Up        | 0.0273       |
| Fumaric acid      | 524          | 1,049         | 2.001908    | Up        | 0.038        |
| Searic acid       | 163,353      | 180,749       | 1.106493    | Up        | 0.0391       |
| **Xylitol**       | 1,103        | 875           | 0.793291    | Down      | 0.0547       |
| Tryptophan        | 49,903       | 27,348        | 0.48023     | Down      | 0.0547       |
| Trans-4-hydroxyproline | 10,342   | 5,637         | 0.545059    | Down      | 0.0547       |
| P-hydroxyphenylactic acid | 700 | 502         | 0.717143    | Down      | 0.0547       |
| Beta-gentibiose   | 1,613        | 2,476         | 1.49783     | Up        | 0.0547       |
| Pantothenic acid  | 8,145        | 2,066         | 0.253653    | Down      | 0.0587       |
| **Urine**         |              |               |             |           |              |
| Uric acid         | 4,621        | 6,056         | 1.310539    | Up        | 0.0039       |
| Kynurenine        | 13,311       | 7,034         | 0.528435    | Down      | 0.0039       |
| Glucoheptulose    | 8,065        | 10,322        | 1.279851    | Up        | 0.0039       |
| 1-Methylinosine   | 7,752        | 4,910         | 0.633385    | Down      | 0.0039       |
| Pseudo uridine    | 1,644,332    | 1,189,538     | 0.723417    | Down      | 0.0078       |
| Isohexonic acid   | 1,798,781    | 115,773       | 0.064362    | Down      | 0.0078       |
| Histidine         | 295,790      | 390,974       | 1.321796    | Up        | 0.0078       |
| Indole-3-lactate  | 21,523       | 7,731         | 0.359197    | Down      | 0.0117       |
| Sucrose           | 7232         | 15,092        | 2.086836    | Up        | 0.0195       |
| Nicotinamide      | 45,119       | 33,991        | 0.753363    | Down      | 0.0195       |
| 7-Methylguanine   | 40,803       | 29,360        | 0.719555    | Down      | 0.0195       |
| 5-Hydroxymethyl-2-furoic acid | 53,570 | 28,530 | 0.532574 | Down | 0.0195 |
| Piceolic acid     | 4,543        | 2,124         | 0.467532    | Down      | 0.0273       |
| 1,3,5-Trimethyluracanic acid | 64,839 | 50,777 | 0.783124 | Down | 0.0273 |
| 1,2-Cyclohexanediol | 40,847  | 28,027       | 0.686146    | Down      | 0.0391       |
| **Uridine$^b$**   | 1,028        | 878           | 0.854086    | Down      | 0.0547       |
| Metanephrine      | 48,104       | 40,710        | 0.846291    | Down      | 0.0547       |
| Ascorbic acid     | 35,228       | 107,869       | 3.062025    | Up        | 0.0547       |

Bold: Metabolite found significant in both pre–post comparison and regression analysis.

*Italic*: $P$ value between 0.05 and 0.06, data included to encourage hypothesis generation.

$^a$P value displayed in table is unadjusted for multiple comparisons. $^b$Metabolite also found to differentiate three response groups.
Systemic steroid response is heterogeneous in preterm infants at risk for severe BPD, and the respiratory response data from this study confirm this. Although pharmacogenomics is beginning to shed light on this variability in drug response, pharmacometabolomic research has the potential to unmask underlying physiology that contributes to drug response variability. In this cohort study, we show that steroid treatment leads to changes in certain serum and urinary metabolites, and that certain metabolite changes are correlated with the degree of respiratory improvement after systemic dexamethasone therapy. Gluconic acid (lactone) is a metabolite that is significant in three of the analyses we performed: it is greatly decreased in serum and gluconic acid lactone in urine.

The most highly associated metabolites were capric acid in serum and gluconic acid lactone in urine.

In the final exploratory analysis, we compared changes in the metabolites among the three steroid response groups: good, moderate, and poor responders. In both serum and urine, none of the metabolites were significantly different among the three groups using a P value of <0.05. However, eight sera (uridine, saccharic acid, p-hydroxyphenylactic acid, phosphoethanolamine, kynurenine, isohexonix acid, gluconic acid, and erythrose) and eight urine metabolites (citrulline, uridine, trehalose, tagatose, mannitol, maltose, alpha-aminoacidic acid, and alloxanoic acid) were different between the three groups using a cutoff of <0.07 (Supplemental Table S1). The patient-specific change in RSS and select metabolites are displayed in Figure 4, with clinical response color-coded as green (good responders), yellow (moderate responders), and red (poor responders). Further research with bigger sample size is needed to investigate the association of these metabolites with degree of steroid response.

***DISCUSSION***

Table 3. Significant association between the baseline metabolite and change in RSS

| Metabolites                | β     | P value | Correlation |
|---------------------------|-------|---------|-------------|
| Serum                     |       |         |             |
| Xylitol                   | −0.00210 | 0.005  | −0.83       |
| N-Acetylcysteine          | −0.00036 | 0.013  | −0.78       |
| Cystine                   | −0.00090 | 0.021  | −0.75       |
| Kynurenic acid            | 0.00242 | 0.035   | 0.70        |
| Saccharic acida           | 0.00000 | 0.001   | −0.89       |
| N-Acetyl-o-tryptophan     | −0.00002 | 0.003  | −0.86       |
| 3,6-Anhydro-d-hexosea     | −0.00052 | 0.004  | −0.85       |
| Uridine                   | −0.00086 | 0.015  | −0.77       |
| Gluconic acid lactonea    | 0.00000 | 0.017   | −0.76       |
| Hexaric acid              | −0.00108 | 0.028  | −0.72       |
| Isoribose                 | −0.00021 | 0.037  | −0.70       |
| Maltotriitol              | −0.00042 | 0.038  | −0.69       |
| Citrulline                | 0.00011 | 0.039   | 0.69        |
| Beta-gentiobiose          | −0.00003 | 0.043  | −0.68       |

RSS, Respiratory Severity Score.
*aChange in metabolite levels associated with change in RSS.*
with steroid therapy, the degree of decrease correlated with the degree of steroid response, and it is nearly significantly different among good, moderate, and poor responders.

Urinary glycolic acid lactone, uridine, and mannitol were found to correlate with degree of steroid response. In all three, the more the metabolite decreased with treatment, the better the clinical response (more negative change in RSS). Gluconic acid (gluconate) is an oxidation product of glucose. The metabolism of glycolic acid is poorly understood in humans, but a recent study of human glucokinase found to correlate with degree of steroid response. In all three, the more the metabolite decreased with treatment, the better the clinical response (more negative change in RSS).

In a model of lung fibrosis, in an animal model of arthritis, direct uridine injection of the joint space prevented development of joint inflammation and inhibited local cytokine production. In ex vivo cell adhesion models and a rat model of chemical-induced lung inflammation, uridine and/or 4-thiouridine decreases leukocyte adhesion, tissue edema, and tumor necrosis factor-alpha levels. A decrease of this anti-inflammatory metabolite with steroid treatment in good responders may indicate the steroids are inhibiting inflammation in the lungs. The metabolite mannitol is thought to arise from the microbiome. Mannitol is produced by lactic acid bacteria, pseudomonal species, and streptococcal species. Mannitol is a biomarker of congestive heart disease, which is increasingly recognized as an inflammatory condition. In total, urine biomarkers associated with degree of steroid response in BPD seem implicated in the inflammatory cascade and oxidative stress, consistent with known disease physiology.

Fanos et al. found that glutonates are one of five metabolites that, in urine samples collected shortly after birth, can distinguish between preterm infants who go on to develop BPD versus those who do not. A study on
the metabolomics of necrotizing enterocolitis showed a marked increase in gluconic acid from urine samples of infants with necrotizing enterocolitis.\textsuperscript{19} Gluconic acid is the only metabolite statistically significantly different in the cord blood of neonates with histologic chorioamnionitis vs. controls, furthering its implication in inflammation.\textsuperscript{20} Thus, a decrease in gluconic acid with steroid treatment in preterm infants with lung disease is consistent with decreased inflammation. The greater the gluconic acid decrease, the better the clinical response to steroids, indicating that this metabolite may be a quantitative biomarker of drug response.

Trans-4-hydroxyproline is decreased in serum after steroid treatment. Trans-4-hydroxyproline is elevated in patients with idiopathic pulmonary fibrosis.\textsuperscript{21} In 14 ventilator-dependent infants with BPD, high-dose dexamethasone treatment was associated with decreased urinary trans-4-hydroxyproline at days 3, 6, 9, and 12 of treatment, indicating suppressed collagen synthesis.\textsuperscript{22} In rats, sepsis-associated lung injury is associated with increased pulmonary fibrosis and hydroxyproline content. In these animals, hydroxyproline was more elevated in animals ventilated with a high tidal volume as opposed to a lower tidal volume, reflective of a more injurious ventilation strategy inducing more lung injury.\textsuperscript{23} In sum, it seems that trans-4-hydroxyproline is a marker of lung injury and fibrosis, so a decrease with steroid treatment is biologically plausible.

Citric acid (citrate) and isocitric acid (isocitrate) were both associated with the degree of RSS improvement after steroid therapy. Both of these molecules are key intermediaries in the tricarboxylic acid cycle, which is an important metabolic pathway for the generation of ATP. If relatively higher levels of citrate and isocitrate are associated with improved lung function, this may imply that with steroid therapy the best responders exhibit quieting of their tricarboxylic acid cycle (and, thus, higher substrate availability), corresponding to less energy demand. Metabolic reprogramming occurs in human and animal models of chronic lung disease, implying that metabolic and energy perturbations may be implicated in BPD development and progression. In patients with BPD and growth failure, resting metabolic expenditure is elevated suggesting increased metabolic demand.\textsuperscript{24}

Gene expression profiles of newborn umbilical cord blood show that infants
who go on to develop BPD have lower levels of genes involved in oxidative phosphorylation and other bioenergetic pathways. 25

Our study has strengths and weaknesses. A strength of our study is the ability to recruit a homogeneous group of preterm infants with severe lung disease and closely phenotype them before and after steroid treatment. Another strength is protocolized and standard dexamethasone dosing in our NICU, so dose variability does not confound our findings. Because extremely preterm infants treated with dexamethasone are rare at our level IV NICU, our sample size is small, and the statistical power is limited. We have not prospectively validated these findings. In addition, because the study was performed during routine clinical care, the timing of the "post" steroid treatment sample was variable (collected when infants were getting blood drawn for clinical reasons). This variability in postdrug sample collection might confound the analysis, but we do not have sufficient sample size to control for this in the current cohort. Last, in this untargeted metabolomic study, we limited statistical analysis to only serum and urine metabolites with known identities. This could prevent our discovery of novel metabolites. Because there is so little known about pharmacometabolomics in neonates, our group felt it important to share this hypothesis-generating type of data while we continue to increase the size of our study cohort. In future research, we hope to secure the funding required for unknown metabolite identification and targeted quantification.

Figure 4. Metabolite change by clinical response group. Left panel displays serum results and right panel displays urine results. For the absolute change in Respiratory Severity Score (RSS) in the top row, each bar represents an individual infant change in RSS with steroid treatment. For the change in metabolite, each bar represents the group mean.
Metabolomics have been used in the neonatal population to identify disease states, such as histologic chorioamnionitis,\textsuperscript{16} early and late-onset sepsis,\textsuperscript{20} cytomegalovirus,\textsuperscript{27} and intraventricular hemorrhage growth restriction.\textsuperscript{28} In addition, metabolomic studies have investigated whether BPD severity and pulmonary hypertension can be predicted from umbilical cord blood metabolomics.\textsuperscript{29} To our knowledge, this is the first study investigating pharmacometabolomics in preterm neonates. The power to understand how changes in biomarkers collected during routine clinical care correlate with likelihood of wanted clinical response to a drug is a potentially powerful tool for precision therapeutics. This study serves as an early investigation of pharmacometabolomics in preterm infants, and the research group is actively expanding the patient cohort to create a fuller understanding of the metabolomics of steroid response in preterm infants.

Supporting Information. Supplementary information accompanies this paper on the Clinical and Translational Science website (www.cts-journal.com).

Table S1.

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