ASSOCIATION OF WEIGHT WITH DRUG DOSING GUIDELINE ADHERENCE IN CHILDREN HOSPITALIZED WITH ASTHMA

A THESIS IN

Bioinformatics

Presented to the Faculty of the University
of Missouri - Kansas City in partial fulfillment of
the requirements for the degree

MASTER OF SCIENCE

by

KATHRYN E. KYLER

M.D., University of Nebraska Medical Center, 2013

Kansas City, Missouri

2019

ASSOCIATION OF WEIGHT WITH DRUG DOSING GUIDELINE ADHERENCE IN CHILDREN HOSPITALIZED WITH ASTHMA

Kathryn E. Kyler, M.D., Candidate for Master of Science Degree

University of Missouri - Kansas City, 2019

ABSTRACT

Background: Obesity can result in physiologic alterations that may be important to drug disposition. Despite this, dosing recommendations for hospitalized children with obesity remain limited, including drugs for asthma exacerbations. This knowledge gap may lead to variability in prescribing practices in children with obesity, posing a serious risk of under or over-exposure to drugs.

Objectives: To examine the prevalence of non-guideline adherent drug dosing by weight in children hospitalized with asthma who are prescribed one of the following commonly used steroid drugs: prednisone, prednisolone, methylprednisolone, or dexamethasone.

Methods and Analysis: We performed a retrospective cohort study of children aged 2-17 years who were prescribed steroids during hospitalization for asthma in the years 2010-2017 using the Cerner Health Facts® (HF) database. The HF database contains de-identified data from more than 500 health care facilities across the US. Doses of 4 commonly prescribed steroid drugs for asthma exacerbation (prednisone, prednisolone, methylprednisolone, and dexamethasone) were categorized as either guideline adherent or non-guideline adherent based on NHLBI asthma guidelines. Non-guideline adherent doses were defined as: doses >

recommended maximum daily dose, 2) total mg/kg/day ≥ 110% of the maximum recommended weight-based dose, or 3) total mg/kg/day ≤ 90% of the minimum recommended weight-based dose. Total daily doses were calculated based on prescribed drug doses and frequencies. Body mass index (BMI) was calculated from documented height and weight; weight categories were defined using age- and sex-specific BMI percentile guidelines established by the CDC. Chi-square tests determined statistical differences in non-guideline adherent doses of all included steroid drugs between weight categories.

Results: We identified 24,155 patients hospitalized for asthma exacerbations who received at least 1 of the included drugs. The majority of patients admitted with asthma exacerbations were aged 6-10 years (44.8%), male (59.8%), African American (51.0%), and had government insurance (55.8%). The majority of children (54%) were a healthy weight. Approximately 38.6% were overweight or obese (n= 9,325); there were 3,648 patients with class I obesity (15.1%), 1,353 with class II obesity (5.6%), and 770 with class III obesity (3.2%). A substantial number of children overall received non-guideline adherent drug doses (27.8%), rising significantly as weight category increased, from 25.2% of the healthy weight group to 41.6% of those with Class III obesity ($p<0.0001$). Weight category remained a significant independent predictor of receiving a non-guideline adherent dose in adjusted logistic regression models ($p<0.0001$).

Conclusion: The association between weight and receipt of non-guideline adherent steroid prescriptions for patients hospitalized with asthma exacerbation increases with increasing weight category, disproportionately affecting children with severe obesity. Future studies should attempt to address differences in hospital clinical and utilization outcomes between patients with and without obesity based on drug dosing differences.

APPROVAL PAGE

The faculty listed below, appointed by the Dean of the School of Medicine have examined a thesis "Association of weight with drug dosing guideline adherence in children hospitalized with asthma," presented by Kathryn E. Kyler, M.D., candidate for Master of Science degree, and certify that in their opinion it is worthy of acceptance.

Supervisory Committee

Kim Smolderen, Ph.D., Committee Chair
Department of Biomedical and Health Informatics

Mark Hoffman, Ph.D.
Department of Biomedical and Health Informatics

Jessica Bettenhausen, M.D.
Division of Pediatric Hospital Medicine, Children's Mercy Kansas City

Matt Hall, Ph.D.
Principal Biostatistician, Children's Hospital Association

TABLE OF CONTENTS

LIST OF ILLUSTRATIONS

Figure Page

LIST OF TABLES

ACKNOWLEDGEMENTS

I would like to thank everyone who was involved with the creation and completion of this study, without whom I would not have been successful in completing this project.

Firstly, I'd like to give a heart-felt thanks to all of my mentors and thesis committee members. Your constant guidance and encouragement were essential to my success.

Second, I need to thank Mr. Earl Glynn and Ms. Sierra Martin, who work as part of the research informatics team at Children's Mercy. They are completing some of the first projects at Children's Mercy using the Health Facts database, including my study. Without their hard work on the front end, I wouldn't have had any data to analyze. The data they provided to me was clean and easy to navigate. Thank you for your hard work.

Lastly, I would like to thank the UMKC School of Medicine for selecting my project for receipt of the Sarah Morrison Student Research Award last fall. The grant funding allowed me to pay for the time of Mr. Glynn, which was helpful in prioritizing my work and enabled me to complete my study on time for a spring 2019 graduation and thesis defense.

CHAPTER 1

INTRODUCTION

Obesity is common in the general and inpatient pediatric populations

Obesity rates continue to climb at alarming rates among children in the United States. Currently, an estimated 18.5% of American children aged 2-19 years have obesity, a rate that has more than tripled since the early 1980s.[1,2] Obesity is defined as a body mass index (BMI) percentile ≥ 95% for age and sex by the Centers for Disease Control (CDC).[3] A sub-classification of obesity has become necessary over the past decade due to continually rising rates and degrees of obesity seen in children (Table 1).[4,5]

Table 1. Pediatric weight category definitions from CDC

Weight Category	Definition
Underweight	BMI percentile <5% for age/sex
Healthy weight	BMI percentile 5% - <85% for age/sex
Overweight	BMI percentile 85% - <95% for age/sex
Obese	BMI percentile 95% or higher for age/sex
Class I obesity	BMI 95% - <120% of the 95th% BMI percentile for age/sex
Class II obesity	BMI 120% - <140% of the 95th% BMI percentile for age/sex
Class III obesity	BMI 140% or higher of the 95th% BMI percentile for age/sex

Obesity affects certain populations more frequently than others, including black and Hispanic children, as well as adolescents.[1] In recent years, there has also been an increase in severe obesity (class II-III obesity) in black and Hispanic children, as well as adolescents.[1] Obesity (and severe obesity to a greater degree) is associated with numerous serious health sequelae, including hypertension, dyslipidemia and atherosclerosis, type 2 diabetes, polycystic ovarian syndrome, sleep apnea, orthopedic complications, post-surgical

complications, hematologic complications (e.g. deep vein thrombosis), and psychosocial stressors (Figure 1).[6–14]

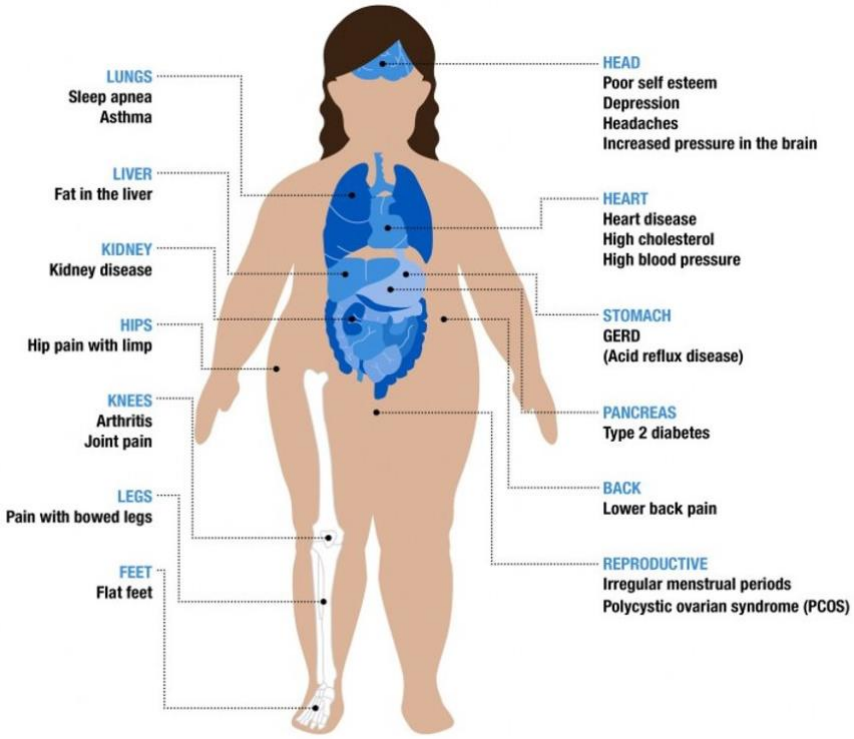

Figure 1. Complications and comorbidities of childhood obesity

Additionally, children with obesity are very likely to become adults with obesity.[15] The risks of obesity as a child are lifelong. Adults who had obesity as a child have an even greater risk of premature death and physical morbidity (e.g. diabetes, hypertension, ischemic heart disease, stroke) in adulthood.[16] The implications of obesity on the health of children are serious, putting them at risk for poor health outcomes as children and throughout their adult life.

Obesity is also associated with increased costs and resource utilization in the outpatient population.[17] Childhood obesity results in approximately $14.1 billion in annual health care spending, encompassing additional cost for prescription drugs, emergency room

care, and outpatient visits.[18] Analysis of the National Inpatient Sample (NIS) database for the years 1999-2005 found that hospital costs related to inpatient hospitalizations with a diagnosis of obesity nearly doubled during the study period, increasing to $237.6 million annually by 2005.[19] These studies illustrate the direct health care-related economic burden childhood obesity places on our national health care system.

Rising Obesity Trend in Pediatric Populations Reflected in Hospital Admissions

While there is a good deal of literature examining trends and characteristics of children with obesity in the general population and guidelines for management of care for this population[1,20,21], fewer studies have examined characteristics and outcomes of hospitalized children with obesity. Prior work describes that obesity may affect an estimated 16-20% of hospitalized children.[22,23] Additionally, there is a growing body of evidence examining specific groups of hospitalized children with obesity, including those in the intensive care unit and those with severe infections or procedural complications.[24–26] Studies describing the effect of obesity in these particular cohorts of inpatients suggest obesity may be associated with increased severity of illness and morbidity, longer length of stay, and higher hospitalization cost.[24–26] However, overall characterization of clinical and demographic characteristics of hospitalized children with obesity has not been thoroughly established.

As such, members of my mentorship team and I have compiled preliminary (as-of-yet unpublished) data from a single tertiary pediatric institution in the Midwest examining the demographic, anthropometric, and clinical characteristics of hospitalized children with obesity. We described in detail the demographic and clinical characteristics of hospitalized

children with obesity as a whole, including what service lines have a higher prevalence of obesity, and what groups of clinical conditions are experienced more frequently by patients with obesity. Overall, we found an increasing prevalence of overweight and obesity over time among hospitalized children consistent with trends seen in the general outpatient population (Figure 2). Approximately 30% of all hospitalized children were overweight, and 15% had obesity. This illustrates the fact that these children make a substantial portion of the pediatric inpatient population and aligns with prior work describing obesity rates in the inpatient population.[22,23] Demographic characteristics were also similar to those found in children with obesity in the general population: children with obesity were more likely to be adolescents, African American or Hispanic, and have government insurance than those without obesity.[1]

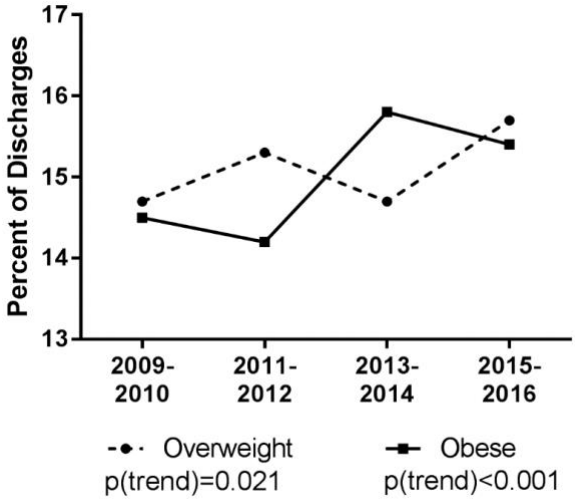

Figure 2. Percent of discharges of patients with overweight and obesity, 2009-2016

We also observed particular service lines and clinical conditions that composed larger proportions of children with obesity than others, including Infectious Diseases (e.g., skin and soft tissue infection), Orthopedics e.g., (non-trauma hip and knee procedures) and

Neurosciences (e.g. seizure) (Figure 3). Asthma, one of the most common reasons for hospitalization in children, and a condition that with a higher prevalence of obesity was the population of interest for my thesis project.[27]

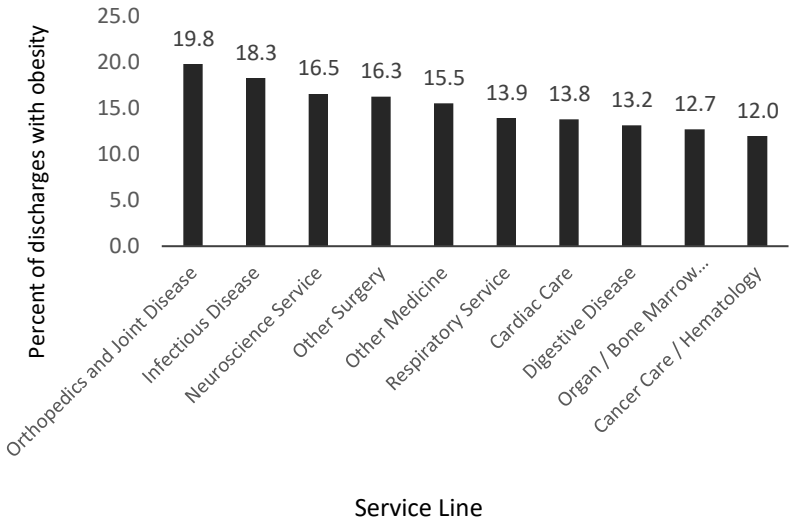

Figure 3. Percent of hospitalizations of patients with obesity by service line

Care Challenges in Children with Obesity

The knowledge gained from our preliminary data was important in development of the study questions because it highlights the frequency of hospital encounters with patients with obesity, and which service lines and diagnoses are most likely to have a greater proportion of patients with obesity. In the hospital setting, children with obesity present unique differences and challenges in administration of equitable care. For example, these patients require different equipment, including larger beds, wheelchairs, gowns, and blood pressure cuffs.[28] Staff caring directly for these patients, particularly those responsible for moving them, require specialized training on proper technique to avoid self-injury, or training in use of special bariatric lifts.

Another unique challenge when caring for patients with obesity is how to address drug dosing. Drugs prescribed to children are most often dosed based on the child's total body weight (TBW).[29] However, very few drugs have evidence-based dosing guidelines that address the increasingly common issue of obesity, due a critical lack of pharmacokinetic knowledge of drugs in children with obesity.[30,31] Patients with obesity are commonly prescribed a wide array of drugs during their hospitalization, with little guidance available regarding if, or how, they should adjust drug dosing for patients with obesity.[31] The growing number of hospitalized children with obesity coupled with the fact that these patients are more likely than those of a healthy weight to experience particular diagnoses highlights the need for evidence-based drug dosing guidelines to direct health care providers to correctly prescribe drugs for this vulnerable population of children.

Why is Inappropriate Medication Dosing A Problem? The Case of Asthma

To illustrate the potential problems that may exist due to lack of pharmacokinetic knowledge and evidence-based drug dosing guidelines in children with obesity, I will use the specific clinical example of children hospitalized with asthma exacerbations. The reasons for examining children hospitalized with asthma are threefold: 1) asthma is one of the most common reasons for hospitalization in children,[27] 2) children with obesity are known to have worse outcomes and symptom control than healthy-weight children,[32,33] and 3) medications prescribed for asthma exacerbations are dosed based on nationally accepted and widely followed National Heart, Lung, and Blood Institute (NHLBI) guidelines and are based on TBW without adjustment for obesity (like most other drugs prescribed to children).[34]

Asthma is the 2nd leading cause for hospitalization among children aged 2-19 years, falling only behind pneumonia.[27] Asthma results in >100,000 pediatric admissions annually, and an estimated annual cost of >$383,000,000 US dollars.[27] We chose to focus on this diagnosis firstly because of the sheer prevalence of hospital admissions in children.

Secondly, outcomes for children with asthma are coupled to their weight status. Children with obesity experience poorer health outcomes associated with both outpatient and inpatient care.[35] For example, children with obesity and asthma are known to have poor asthma control scores compared to children of healthy weights, have more frequent office and emergency room visits, and be poor responders to inhaled drugs used to treat asthma.[32,33,36]

Finally, we selected children hospitalized for asthma exacerbations as our population of interest because the drug dosing recommendations for steroids commonly prescribed during asthma exacerbations are well-defined.[34] All of the drug dosing recommendations for asthma are dosed based on the child's TBW, without adjustments for children with obesity. The most commonly followed drug dosing guidelines for asthma in children were released by the NHLBI in 2007.[34] The dosing recommendations for prednisone, prednisolone and methylprednisolone for asthma exacerbations are included in this guideline.

The dosing for dexamethasone, another steroid drug commonly prescribed for treatment of asthma, is not included in the NHLBI guidelines. Most of the evidence supporting use of dexamethasone for asthma exacerbations has been published in the years following the most recent iteration of the NHLBI guidelines. We chose to include dexamethasone in addition to other steroids outlined by the NHLBI because it is commonly utilized for asthma exacerbation.[37,38] Current available evidence supports dosing of the drug

at 0.6 mg/kg/dose, given in a single dose once, with potential for repeat dosing at the same strength the following day.[39]

Obesity causes physiologic changes that may affect drug disposition

Many pediatric clinical pharmacologists postulate that significant alterations in various physiologic properties and functions noted in children with obesity may lead to substantial changes in drug disposition, including differences in drug absorption, distribution, metabolism, and excretion (Figure 4).[29,30] For example, the volume of distribution of a drug varies greatly based on the make-up of an individual's body habitus, particularly adiposity.[29] The shift in adipose-to-lean body mass ratios associated with obesity leads to significant differences in measures used to predict drug distribution and clearance. In addition, individuals with obesity have increased cardiac output, altered blood flow through the liver, altered function of various Cytochrome P450 enzymes, and increased glomerular filtration rate, all of which could affect drug disposition in children with obesity.[29,30,40] These changes in physiologic properties may lead to significant alterations in drug exposure in an individual with obesity, and may necessitate dosing adjustments to either achieve desired efficacy or prevent unwanted toxicities.

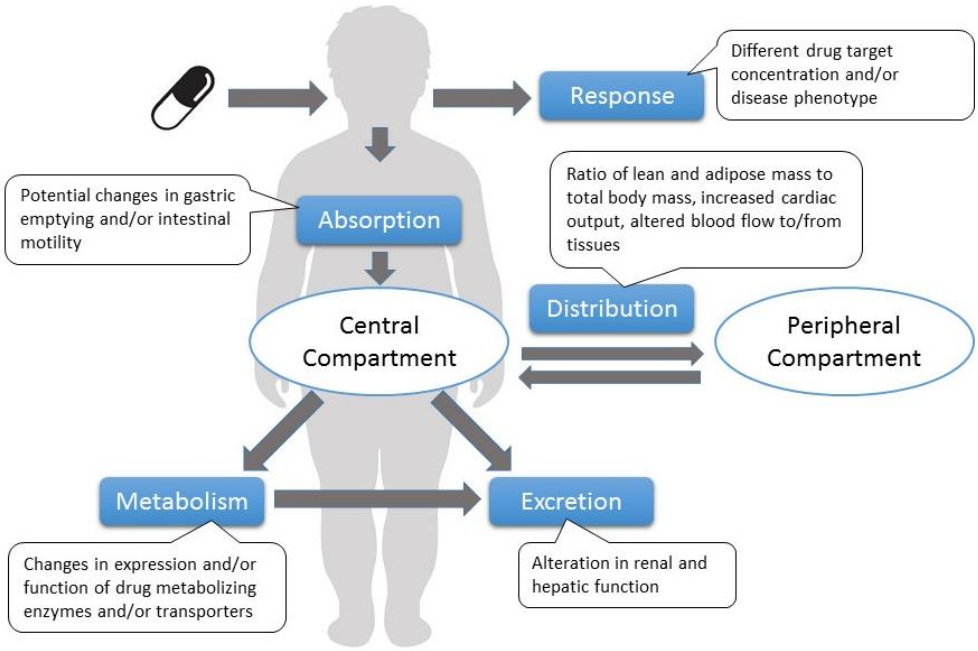

Figure 4. Pharmacokinetic alterations as a result of obesity

Limited pharmacokinetic data exists for steroids prescribed for asthma exacerbations

There is a critical lack of pharmacokinetic information for the majority of commonly prescribed drugs in hospitalized children with obesity.[31] Very little pharmacokinetic evidence exists for the steroid drugs of interest in this study. Previous pharmacokinetic work, primarily in adults, explains that individuals with obesity have altered pharmacokinetics of oral steroids compared to non-obese control subjects, including poor oral absorption and increased clearance leading to decreased efficacy.[36,41] In theory, the relative hypercortisolemia experienced by individuals with obesity at baseline could affect exogenous steroid effects.[42] Children with asthma and obesity have worse asthma-related health outcomes, including poorer symptom control and a greater likelihood of oral steroid courses for exacerbations.[32,35] These findings may be the result of the pharmacokinetic changes seen in this population.

Variability in care negatively affects health outcomes in hospitalized children

Increasing the pharmacokinetic knowledge available regarding commonly prescribed drugs in hospitalized children with obesity will ultimately lead to improved health outcomes in this population through implementation of targeted, evidence-based drug dosing guidelines that include specific recommendations for children with obesity. Prior work has shown that variability negatively impacts hospital outcomes.[43,44] Implementation of evidence-based clinical practice guidelines (including drug dosing recommendations), may help improve these outcomes.[43,44] An understanding of how the current lack of guidance affects variability in prescribing habits for patients with obesity hospitalized with asthma is an important first step in identification of drugs and patients most at-risk of adverse events as a result of drug under- or over-exposure. My goal by completing this project is to begin to understand how drug prescribing practices vary for children hospitalized with asthma exacerbation who have obesity versus those of a healthy weight.

Study Objectives and Hypotheses:

Based on the lack of pharmacokinetic data driving evidence-based drug dosing guidelines for children, we hypothesize that inconsistencies in prescribing practices exist for children of varying weight categories. This variability may lead to negative downstream impacts on the health of children with obesity as a result of over- or under-exposure to commonly prescribed drugs, such as steroids prescribed during asthma exacerbations. Children at the extreme of the weight spectrum (i.e. children with obesity) may be at greatest risk of these negative effects, as there are no dosing guidelines to direct prescribers specifically in their weight category.

Therefore, our overall research objective was to determine if children with obesity have a different likelihood of receiving drug doses outside of recommended dosing guidelines by comparing outcomes across weight categories (underweight, healthy weight, overweight, and obese) in children 2-17 years of age hospitalized with asthma exacerbations. This was accomplished by execution of the following objectives:

Objective 1: For each steroid drug commonly prescribed for inpatient asthma exacerbations (i.e., prednisone, prednisolone, methylprednisolone, dexamethasone), determine the percent of children prescribed a dose that does not adhere to available dosing guidelines by weight category.

Hypothesis 1: The percent of children who receive a dose non-adherent to the national dosing guidelines will be greater for children in the obese weight category vs healthy-weight.

Objective 2: To identify patient-level factors (e.g., demographic characteristics, weight category) associated with non-adherence to available dosing guidelines.

Hypothesis 2: Children with obesity and older children will be more likely to receive a non-guideline adherent drug dose than children with other patient-level factors.

Objective 3: To identify hospital-level factors associated with non-adherence to available dosing guidelines.

Hypothesis 3: Hospital annual pediatric case volume and hospital type will be significantly more likely to influence non-adherence to dosing guidelines than other hospital-level factors.

CHAPTER 2

METHODS

Study Design and Patients

To accomplish my objectives, we designed a retrospective cross-sectional comparative study of children with and without obesity hospitalized with an asthma exacerbation using the Cerner Health Facts® database. This study was approved as non-human subjects research by the Children's Mercy Institutional Review Board on 11/14/2018.

Data Collection and the Database

A multi-center database of hospitalized children with asthma was compiled using data from the Cerner Health Facts® database for the years 2010-2017. This time period captures all recent years during which *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10) codes were the primary diagnosis codes in use (2015-2017), and the preceding years with adequate data quality for children in the Health Facts database.

The Cerner Health Facts® database is one of the largest electronic health records databases in the US, and is ideal for completion of this study for several reasons. The database includes de-identified, HIPAA-compliant data from more than 500 health care facilities across the United States representing 64 million unique patients and 415 million patient encounters over the past two decades. Health Facts® data are publicly available, and maintained by the Cerner Corporation (Kansas City, MO). The database includes administrative data (diagnosis coding, billing data, demographic information) and contains detailed patient-level clinical data, including anthropometric measures and drugs prescribed

(e.g. dosing and timing of administration), which are imperative to answering clinical questions like those posed for this study.

Study Population

All children aged 2-17 years admitted (inpatient or observation) with a principal discharge diagnosis of asthma exacerbation to any Health Facts® health care facility during the years 2010-2017 were included. Asthma exacerbation hospitalizations were identified using a principle diagnosis *International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification* (ICD-9/10) codes for asthma exacerbation (Table 2).

Table 2: Asthma ICD-9/10 Codes

ICD-9 Codes	ICD-10 Codes
493.00-493.02	J45.20-J45.32
493.10-493.12	J45.40-J45.52
493.20-493.22	J45.90-J45.909
493.81-493.92	J45.99-J45.998

If weight and height were unavailable for a child in a given encounter, then they were excluded from analysis. Children with an ICD-9/10 code for pregnancy or childbirth, hospital encounters that were mortalities, or children who did not receive at least one of the included steroid drugs (i.e., prednisone, prednisolone, methylprednisolone, dexamethasone) were excluded. For this study, obesity was defined according to the current CDC classification system for children, which uses BMI percentile for age and sex to categorize patients' weight category (Table 3).[5] To allow comparison across groups, BMI data was then used to categorize each child according to their weight category: underweight, healthy weight, overweight, class I obesity, class II obesity, and class III obesity.

Table 3: Weight category definitions

Weight Category	Definition
Underweight	BMI percentile <5% for age/sex
Healthy weight	BMI percentile 5% - <85% for age/sex
Overweight	BMI percentile 85% - <95% for age/sex
Obese	BMI percentile 95% or higher for age/sex
Class I obesity	BMI 95% - <120% of the 95th% BMI percentile for age/sex
Class II obesity	BMI 120% - <140% of the 95th% BMI percentile for age/sex
Class III obesity	BMI 140% or higher of the 95th% BMI percentile for age/sex

Measures

Pertinent patient- and hospital-level data, spanning more than 500 health care facilities across the country, were extracted from the Health Facts® database and served as the inception cohort for this investigation (Table 4).

Table 4. Patient- and hospital-level measures

Patient-level Information	Hospital-level Information
Patient identification number	Census region
Date of admission	Hospital type (tertiary vs. community hospital)
Date of discharge	Urban vs. rural location
Age (years)	
Race/Ethnicity	
Sex	
Insurance payer	
Weight	
Height	
Body mass index (BMI)	
Drug name	
Drug dose and frequency	
Discharge diagnosis codes	

Drug Selection

For analysis of drugs used during asthma exacerbation hospitalizations, we chose the most commonly prescribed non-inhaled drugs based on asthma treatment guidelines and examination of the most commonly prescribed drugs at children's hospitals reporting data to the Pediatric Health Information System (PHIS) database. The PHIS database is a HIPAA compliant, de-identified database containing clinical and resource utilization data from more than 45 children's hospitals around the United States. We identified the following steroids most frequently prescribed to children hospitalized with asthma exacerbation: prednisone, prednisolone, methylprednisolone, and dexamethasone.

Appropriate weight-based dosing was selected using commonly referenced guidelines from the NHLBI (Table 4).[34] Dexamethasone dosing is currently based on an individual's total body weight (TBW), without adjustments for weight category (Table 5).[39] Some studies have suggested that ideal body weight or lean body weight may be more appropriate for dosing of certain drugs (e.g., dexamethasone)[45], however, for the purposes of this study we utilized TBW-based dosing based on current national guidelines and commonly referenced clinical resources (e.g., Lexicomp®) as it is the most commonly employed dosing scheme at our institution. This dosing is based on several studies examining efficacy of dexamethasone compared to prednisolone or prednisone in children hospitalized with asthma exacerbations.[37–39] We chose to exclude inhaled drugs (e.g. bronchodilators, inhaled corticosteroids), as dosing protocols vary significantly by institution and there are no national dosing guidelines for drugs.

Table 5: NHLBI asthma guideline recommended steroid dosing[15]

Drug	TBW-based Dosing	Maximum Daily Dose
Prednisone	1-2 mg/kg/day	Age ≤ 12 years: 60 mg; Age ≥ 13 years: 80 mg
Prednisolone	1-2 mg/kg/day	Age ≤ 12 years: 60 mg; Age ≥ 13 years: 80 mg
Methylprednisolone	1-2 mg/kg/day	Age ≤ 12 years: 60 mg; Age ≥ 13 years: 80 mg
Dexamethasone	0.6 mg/kg/dose	16 mg

Doses categorized as non-adherent to available guidelines will be defined as[46,47]:

- Dose over the absolute recommended maximum daily dose
- Total mg/kg/day or mg/kg/dose ≥ 110% of the maximum recommended TBW-based dose for children
- Total mg/kg/day or mg/kg/dose ≤ 90% of the minimum recommended TBW-based dose for children

We chose parameters utilized in other literature[46,47] of a single or daily dose ≥ 110% of the maximum recommended dose, or a single or daily dose ≤ 90% of the minimum recommended dose based on a child's weight, because younger children may not be heavy enough to reach the maximum adult dose based on their TBW-based dose. Using mg/kg dosing, younger children (i.e., <12 years old) are less likely to reach or exceed the maximum adult dose, as their absolute TBW, regardless of obesity status, is still likely to be below that of an average adult weighing 70kg.

Statistical Analysis

Sample Size and Power Calculation

Under the assumption that the healthy weight group will receive doses that adhere to prescribing guidelines 95% of the time[48], and that non-healthy weight groups will receive doses that adhere to prescribing guidelines 90% of the time, we will need 582 children in each group to detect a difference via two-sided chi-square test with 90% power. No pilot data or prior studies are available at the point of undertaking this study to create more detailed sample size or effect size estimates. However, we anticipated that we would find a substantially larger number of subjects meeting inclusion criteria using the Health Facts® database based on the number of potential encounters included in the database and the fact that asthma is one of the most common reasons for admission in pediatrics. Therefore, we did not anticipate problems reaching adequate numbers of patients meeting our inclusion criteria using this methodology.

Statistical Analysis

All data were analyzed on the encounter level, because while many patients with asthma will have repeat admissions during their childhood, each admission encounter represents a new and different opportunity to assess patient-, provider-, and hospital-level variation in prescribing practices.

We calculated descriptive statistics (frequencies, means, proportions) for each encounter to provide an accurate illustration of our final cohort (Table 6). First, descriptive statistics were calculated for encounter-level demographic characteristics: age group (2-5 years, 6-10 years, 11-14 years, 15-17 years), sex (male, female), race (non-Hispanic black, non-Hispanic white, other, unknown), and insurance payer. We also calculated descriptive statistics by encounter for patient anthropometric (i.e. weight) category based on the above described CDC guidelines: underweight, healthy weight, overweight, class I obesity, class II

obesity, and class III obesity. BMI was calculated from recorded weight and height measurements as described above. Lastly, descriptive statistics were calculated to illustrate the hospital-level characteristics by encounter: census region, teaching facility designation, and urban vs. rural location.

Table 6: Patient- and hospital-level factors to be included in analysis

Patient-level Factors	Hospital-level Factors
Age	Census region
Race/Ethnicity	Teaching hospital designation (Yes vs. No)
Sex	Urban vs. Rural Location
Insurance payer	
Weight category	

For all categorical variables, chi-square tests were utilized to compare patient- and hospital-level characteristics across weight groups, to evaluate for statistical differences between groups based on weight group. The chi-square test is a non-parametric statistical test used to compare group differences or associations between categorical variables (e.g. demographic, anthropometric, and hospital-level characteristics of our cohort). All assumptions required for performance of chi-squared tests were met, including: 1) all variables were nominal (categorical), 2) all observations were independent, and 3) all expected frequencies were >5. Statistical significance was established as an alpha level of <0.05.

For our main outcome analysis, we analyzed patients that received the drugs of interest at the encounter level. We compared the proportion of children who received a drug dose that did not adhere to recommended dosing guidelines (non-guideline adherent dose) during their hospitalization across weight groups using a chi-square statistic. We performed

this analysis in aggregate for all the included drugs, and independently for each of the drugs. Once again, all assumptions for performance of the chi-square test were met (see above).

Comparisons of proportions of non-guideline adherent dose rates between demographic groups and by hospital-level characteristics were also completed using chi-square tests.

Lastly, we performed multivariable logistic regression modeling incorporating all patient-and hospital-level variables found to be significant predictors of receiving a non-guideline adherent dose in chi-square analyses. All assumptions for performance of the multivariable logistic regression model were met:

1) Dependent variable is categorical and binomial (guideline adherent dose vs. non-guideline adherent dose).
2) All observations were independent of each other.
3) The independent variables showed minimal collinearity. All variables were categorical; however, multiway frequency analyses were completed to test for associations between independent variables. Many of them were significantly associated with one another. However, the associations between weight, demographic and geographic characteristics is well-known.[1] The social determinants of health (e.g. socioeconomic status, access to health care, etc.) have a major impact on the vast majority of the included independent variables.
4) There were no significant outliers in this analysis, as all included variables were categorical in nature. Prior to analysis any significant outliers for weight and

height were removed using established guidelines from the CDC for biologically implausible values.[49]

5) All independent variables in this analysis were nominal, so there was no need to test for linearity of relationship of any continuous independent variables to the logit of the dependent variable.

Data Extraction Process

Our database was compiled from the Cerner Health Facts database over a series of extraction iterations spanning several weeks. The work of data extractions and cleaning was support by the Sarah Morrison Student Research Award, a grant awarded to Dr. Kyler from the University of Missouri-Kansas City in 2018. The award resulted in a partnership with a team of data informaticists at Children's Mercy Hospital, namely Dr. Mark Hoffman and Mr. Earl Glynn.

The necessary data elements were obtained from the Health Facts database. Data were organized into two primary databases for analysis: one Encounter-based file, and one Medication-based file. The Encounters file contained all patient identification and demographic data, and hospital-level data for each encounter for every encounter meeting our inclusion criteria: 1) primary discharge diagnosis of asthma, 2) age 2-17 years, 3) admit year 2010-2017. Additionally, it contained the patient anthropometric data, including recorded heights, weights, and BMIs. The Medications file contained all included drugs prescribed in a given encounter to any patient meeting the above-mentioned inclusion criteria. Prescription details were also recorded in this database, including drug dose (strength in mg), and frequency (how often the drug was to be given).

CHAPTER 3

RESULTS

Cohort Identification

Based on our initial inclusion criteria of all children aged 2-17 years hospitalized with asthma exacerbation (with an encounter time > 0 minutes) in the years 2010-2017, we identified 31,154 patient encounters for potential analysis (Figures 5-7). We then completed the process of removing incomplete or inconsistent data from both the Encounters file and Medications file.

First, within the Encounters file, biologically implausible BMI values (n=286), likely as a result of inconsistencies in recorded weights or heights, were excluded. Biologically implausible BMI values are defined by the CDC as BMI values outside the expected extremes of standard deviations (z-scores) based on data from the National Health and Nutrition Examination Survey (NHANES).[49] Next, 2,970 encounters were excluded because there was no recorded weight in the encounter. Finally, 3,742 encounters were eliminated for lack of prescriptions of included steroid drugs, leaving 24,155 encounters for inclusion in our analysis (Figure 7).

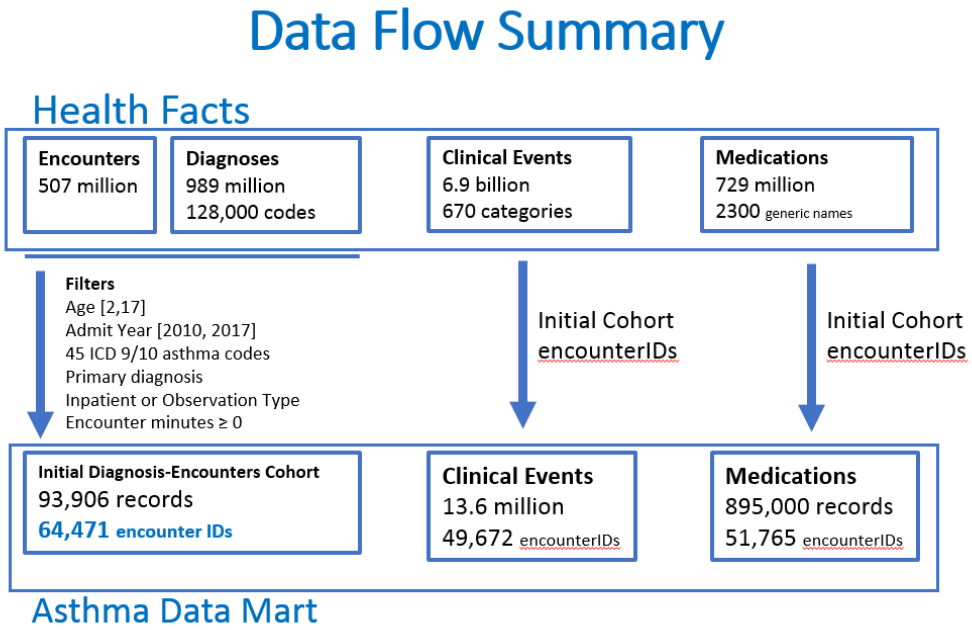

Figure 5. Data flow summary for initial data extraction from Health Facts database

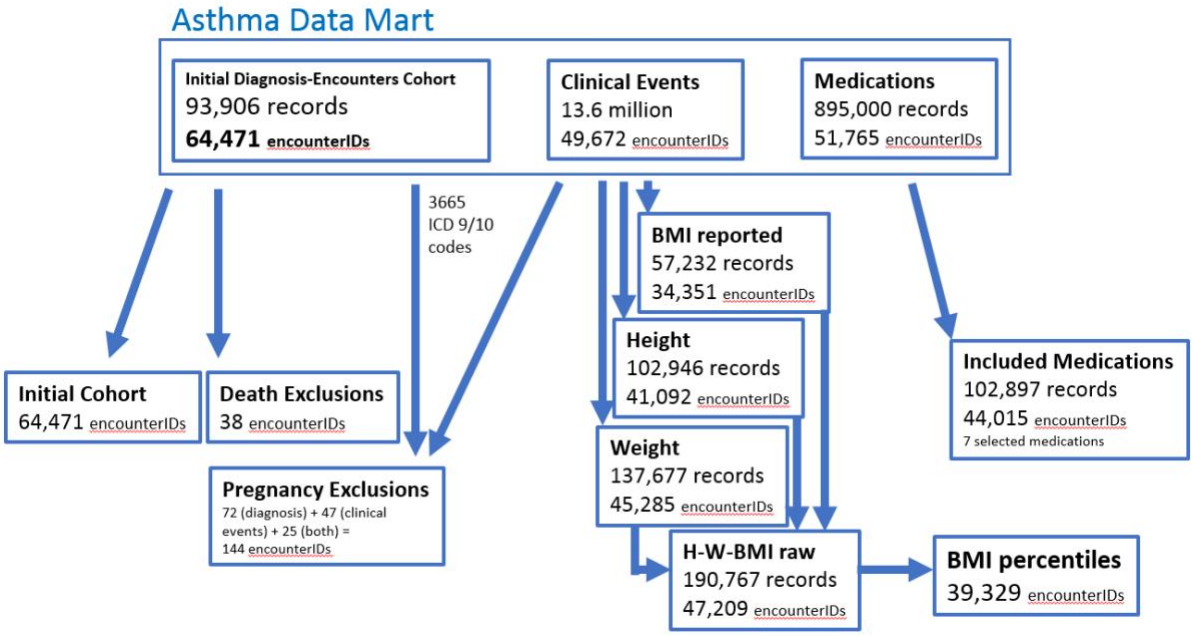

Figure 6. Data flow summary for initial data extraction from Health Facts database

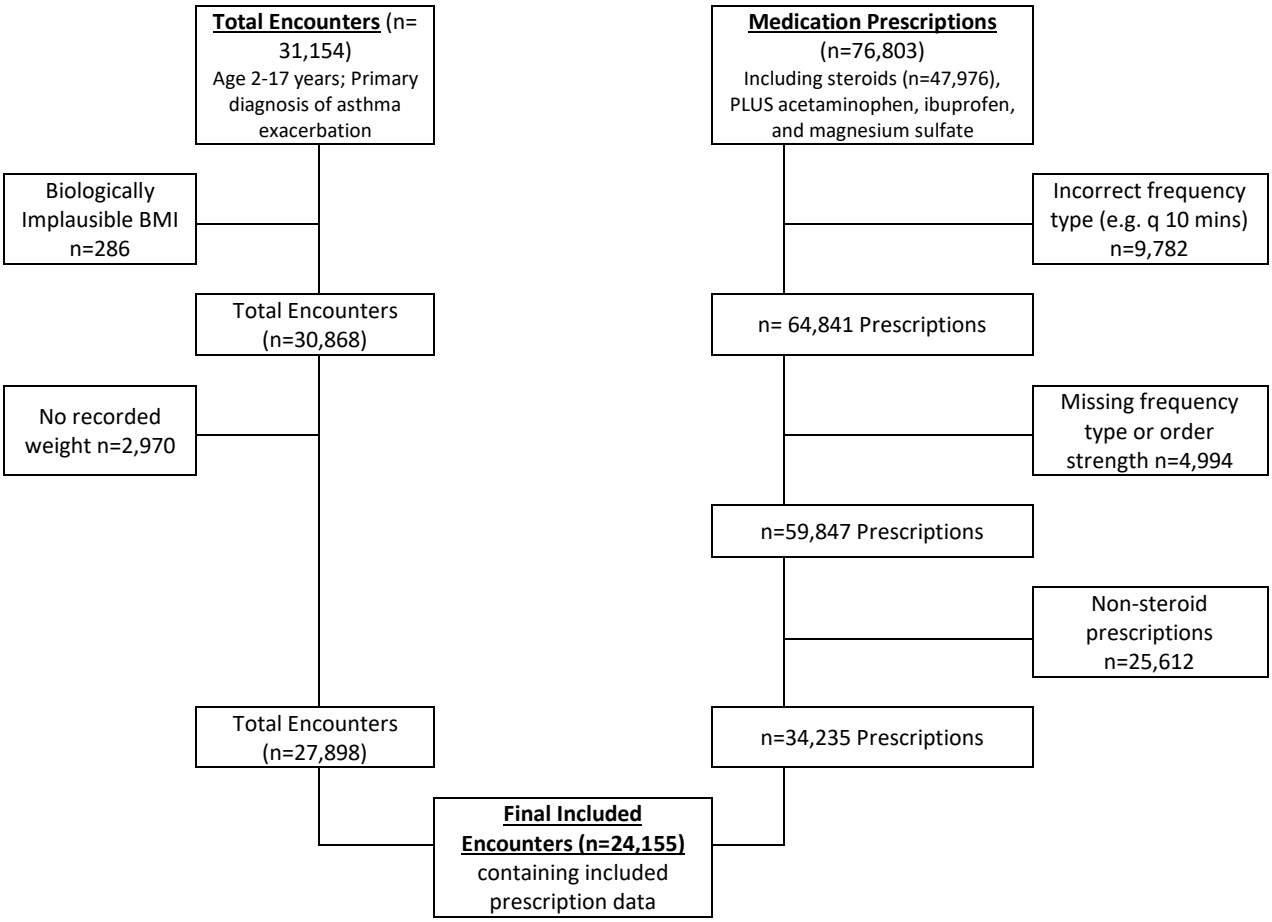

Figure 7. STROBE diagram

Of the initially included prescription data in the Medications file (n=74,623), cases were excluded for missing dose frequency data (n=2,653), missing order strength data (n=2,341), or if the prescribed frequency was not included for analysis (n=9,782) (Table 7). An additional 25,612 non-steroid prescriptions (acetaminophen, ibuprofen, magnesium sulfate) were excluded, ultimately leaving a total of 34,235 prescriptions of included steroids for analysis in our 24,155 encounters.

Table 7: Included and excluded prescription frequency data

Included frequencies	Excluded frequencies
Once	Unknown/Invalid/Not Mapped
Daily	Specified Interval/At specific time
Twice daily/every 12 hours	Stat
Three times daily/every 8 hours	With meals
Four times daily/every 6 hours	Every other day
Six times daily/every 4 hours	MWF
	PRN
	Pre-op
	Every 1 hour
	Every 2 hours
	Every 10 minutes

Cohort Characteristics

We identified 24,155 patients aged 2-17 years hospitalized for an asthma exacerbation during the years 2010-2017. The majority were aged 6-10 years (45.2%), male (60.2%), non-Hispanic Black (50.6%), and had government insurance (55.7%) (Table 8). Only 19.4% of included patients had private insurance, with 12% listed as "Other" and an additional 12% as "Unknown". Some examples of insurance plans in the "Other" insurance category included HMO and PPO plans that were not categorized as either government or commercial, and self-pay. "Unknown" insurance types were unknown, unmapped in the Health Facts database, or invalid.

Table 8. Demographics

		Overall	Underweight	Healthy	Overweight	Class I Obesity	Class II Obesity	Class III Obesity	p-value
	Overall	24155	1790 (7.4)	13040 (54.0)	3554 (14.7)	3648 (15.1)	1353 (5.6)	770 (3.2)	
Age	2-5 years	8656 (35.8)	996 (11.5)	5053 (58.4)	1046 (12.1)	1217 (14.1)	273 (3.2)	71 (0.8)	<.0001
	6-10 years	10822 (44.8)	639 (5.9)	5887 (54.4)	1694 (15.7)	1581 (14.6)	649 (6.0)	372 (3.4)	
	11-14 years	3234 (13.4)	107 (3.3)	1446 (44.7)	602 (18.6)	583 (18.0)	288 (8.9)	208 (6.4)	
	15-17 years	1443 (6)	48 (3.3)	654 (45.3)	202 (14.7)	267 (18.5)	143 (9.9)	119 (8.3)	
Gender	Male	14451 (59.8)	1128 (7.8)	7859 (54.4)	2031 (14.1)	2193 (15.2)	784 (5.4)	456 (3.2)	0.0007
	Female	9704 (40.2)	662 (6.8)	5181 (53.4)	1523 (15.7)	1455 (15.0)	569 (5.9)	314 (3.2)	
Race	Non-Hisp White	71925 (29.8)	536 (7.5)	3845 (53.5)	1084 (15.1)	1137 (15.8)	364 (5.1)	226 (3.1)	<.0001
	Non-Hisp Black	12308 (51.0)	879 (7.1)	6859 (55.7)	1767 (14.4)	1725 (14.0)	668 (5.4)	410 (3.3)	
	Other	1647 (6.8)	149 (9.1)	833 (50.6)	237 (14.4)	262 (15.9)	123 (7.5)	43 (2.6)	
	Unknown	3008 (12.5)	226 (7.5)	1503 (50.0)	466 (15.5)	524 (17.4)	198 (6.6)	91 (3.0)	
Payor	Government	13475 (55.8)	962 (7.1)	7293 (54.1)	1945 (14.4)	2061 (15.3)	773 (5.7)	441 (3.3)	0.0016
	Private	4681 (19.4)	372 (8.0)	2572 (55.0)	689 (14.7)	699 (14.9)	231 (4.9)	118 (2.5)	
	Other	2977 (12.3)	260 (8.7)	1554 (52.2)	450 (15.1)	430 (14.4)	185 (6.2)	98 (3.3)	
	Unknown	3022 (12.5)	196 (6.5)	1621 (53.6)	470 (15.6)	458 (15.2)	164 (5.4)	113 (3.7)	

Of the included 24,155 encounters, 20,359 (92.5%) were made up of patients with only a single hospitalization encounter during the study period. The remaining 3,796 encounters were for patients that had between 2 and 14 encounters for asthma exacerbation during the study period.

Overall, encounters occurred at 152 hospitals, encompassing 136 health systems around the United States. Of the 152 included hospitals, 12 (7.9%) had >500 included encounters during the study period. The maximum number of encounters per hospital was 4,855. The median number of encounters was 9 per facility, indicating a large number of hospitals had very few encounters over the study period. The included encounters were geographically diverse, with 11,965 (49.5%) located in the southern US, 4,929 (20.4%) located in the Northeast, 4,725 (19.6%) in the Midwest, and 2,536 (10.5%) in the West. A total of 17,750 encounters (86.5%) occurred at hospitals identified as teaching facilities. 20,016 (82.9%) were located in urban areas.

Weight Categories

The majority of included patients had a healthy weight status (n=13,040, 54%) (Figure 8). Approximately 38.6% had overweight or obesity (n= 9,325), with 3,648 patients having class I obesity (15.1%), 1,353 with class II obesity (5.6%), and 770 with class III obesity (3.2%). Only 1,790 (7.4%) of included patients were underweight.

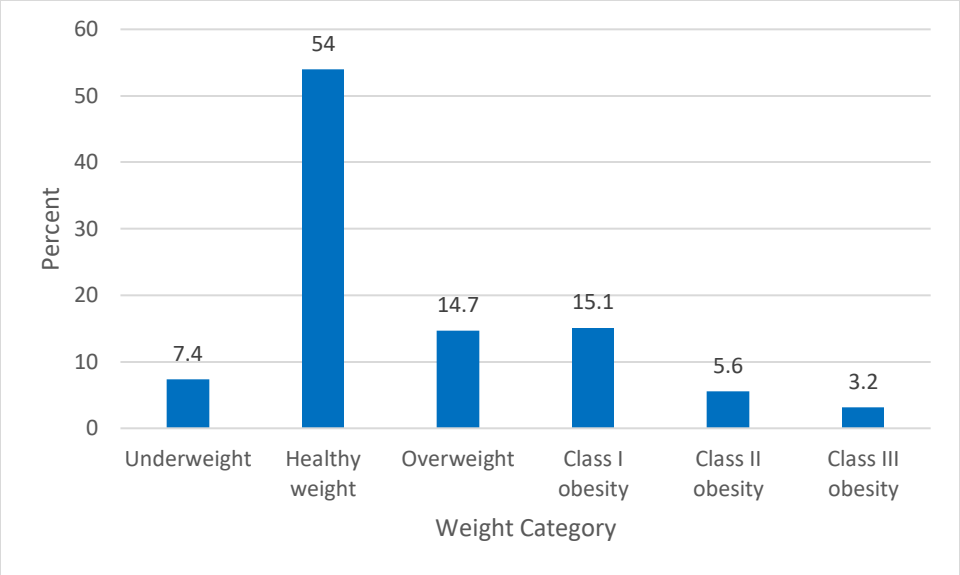

Figure 8. Weight status of included patients

Prescription Characteristics

We analyzed a total of 34,235 steroid prescriptions, including 14,216 (41.5%) for prednisolone, 7,314 (21.4%) for prednisone, 7,728 (22.6%) for methylprednisolone, and 4,977 (14.5%) for dexamethasone. Prednisolone and dexamethasone were more likely to be prescribed to younger children ($p<0.0001$), and methylprednisolone and prednisone were more likely to be prescribed to older children ($p<0.0001$). Every included patient encounter was prescribed at least one of these drugs, with some encounters having more than one included prescription (n=10,080, 29.4%).

Unadjusted proportions of non-guideline adherent steroid prescriptions

For our primary outcome analysis, we found that overall, 6,702 (27.8%) encounters were prescribed a non-guideline adherent drug dose (Figure 9). The steroid with the largest proportion of patients receiving a non-guideline adherent prescription was methylprednisolone (n=3,485, 45.1%). The steroid with the lowest rates of non-guideline

adherence was prednisolone (n=1,080, 7.6%). We found a significant increase in the proportion of children prescribed non-guideline adherent drug doses as weight class increased, from 3,286 (25.2%) of children with a healthy weight, up to 320 (41.6%) of children with class III obesity ($p<0.0001$, Cramer's V=0.1) (Figure 9).

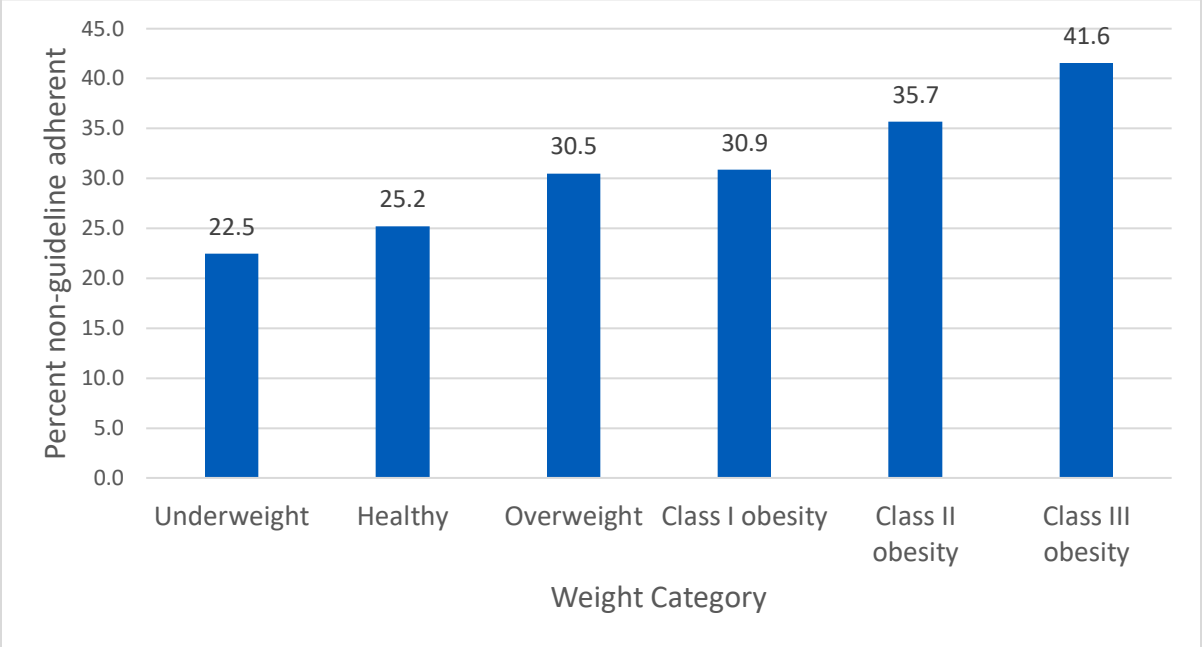

Figure 9. Proportion of encounters receiving non-guideline adherent drug prescription

Other factors associated with receiving non-guideline steroid prescription

In addition to increased risk of non-guideline adherent prescriptions as weight class increased, there were many other factors associated with receiving a non-guideline adherent steroid prescription. We found older patients (aged 15-17 years, 47.7% non-guideline adherent prescription), females (28.7%), African American or Caucasian race (both 28.1%), and those with government or other insurance (29.4% and 31.4%, respectively) had higher rates of non-guideline adherent steroid prescriptions than children with other demographic

characteristics (all p<0.0067) (Table 9). Cramer's V effect sizes for age, sex, race, and insurance were 0.19, 0.02, 0.03, and 0.08, respectively.

Table 9. Proportion of encounters receiving non-guideline adherent drug prescription by demographic characteristics

		Overall	Non-GA dose	p-value	Cramer's V
N		24155	6702 (27.8)		
Age	2-5 years	8656 (35.8)	1765 (20.4)	<0.0001	0.19
	6-10 years	10822 (44.8)	2851 (26.3)		
	11-14 years	3234 (13.4)	1398 (43.2)		
	15-17 years	1443 (6.0)	688 (47.7)		
Gender	Male	14451 (59.8)	3917 (27.1)	0.0067	0.02
	Female	9704 (40.2)	2785 (28.7)		
Race/Ethnicity	Non-Hisp White	7192 (29.8)	2020 (28.1)	0.0006	0.03
	Non-Hisp Black	12308 (51.0)	3457 (28.1)		
	Other	1647 (6.8)	384 (23.3)		
	Unknown	3008 (12.5)	841 (28.0)		
Payer	Government	13475 (55.8)	3966 (29.4)	<0.0001	0.08
	Private	4681 (19.4)	1192 (25.5)		
	Other	2977 (12.3)	935 (31.4)		
	Unknown	3022 (12.5)	609 (20.2)		

Hospital-level characteristics associated with non-guideline adherent prescriptions included: region, urban/rural location, and whether or not the hospital was a teaching institution (all p<0.0001) (Table 10). Encounters in the West had the highest proportion of encounters receiving a non-guideline adherent prescription (34.2%), and those in the Midwest were the lowest (16.4%). Of note, encounters in the West had the highest rates of prescribing dexamethasone and those in the Midwest prescribed the most prednisolone. Encounters occurring at a teaching institution had lower rates of prescribing a non-guideline adherent steroid dose (29.2% vs 40.5% in non-teaching hospitals).

Table 10. Proportion of encounters receiving non-guideline adherent drug prescription by hospital-level characteristics

		Overall	non-GA dose	p value	Cramer's V
N		24155	6702 (27.8)		
Region	South	11965 (49.5)	3914 (32.7)	<0.0001	0.15
	Northeast	4929 (20.4)	1147 (23.3)		
	Midwest	4725 (19.6)	773 (16.4)		
	West	2536 (10.5)	868 (34.2)		
Academic Center*	Yes	17750 (86.5)	5174 (29.2)	<0.0001	0.08
	No	2760 (13.5)	1117 (40.5)		
Rural vs Urban	Urban	20016 (82.9)	5420 (27.1)	<0.0001	0.03
	Rural	4139 (17.1)	1282 (31.0)		

We examined each individual non-guideline adherent steroid prescription to determine if patients receiving these prescriptions were under- or over-dosed according to guidelines/standards. Prednisolone doses were the least frequently found to be non-guideline adherent in general (Table 11) and were equally under-dosed (2.5%) and overdosed (5.1%) (Figure 10). Methylprednisolone was more often over-dosed (42.6% vs 2.5% under-dosed). Prednisone and dexamethasone was more often under-dosed (21.7% under-dosed vs 12.6% over-dosed).

Table 11. Proportion of non-guideline adherent prescriptions by drug

	Overall	non-GA dose	p value	Cramer's V
Prednisolone	14216 (41.5)	1080 (7.6)	<0.0001	0.36
Prednisone	7314 (21.4)	1284 (17.6)		
Methylprednisolone	7728 (22.8)	3485 (45.1)		
Dexamethasone	4977 (14.5)	1595 (32.1)		

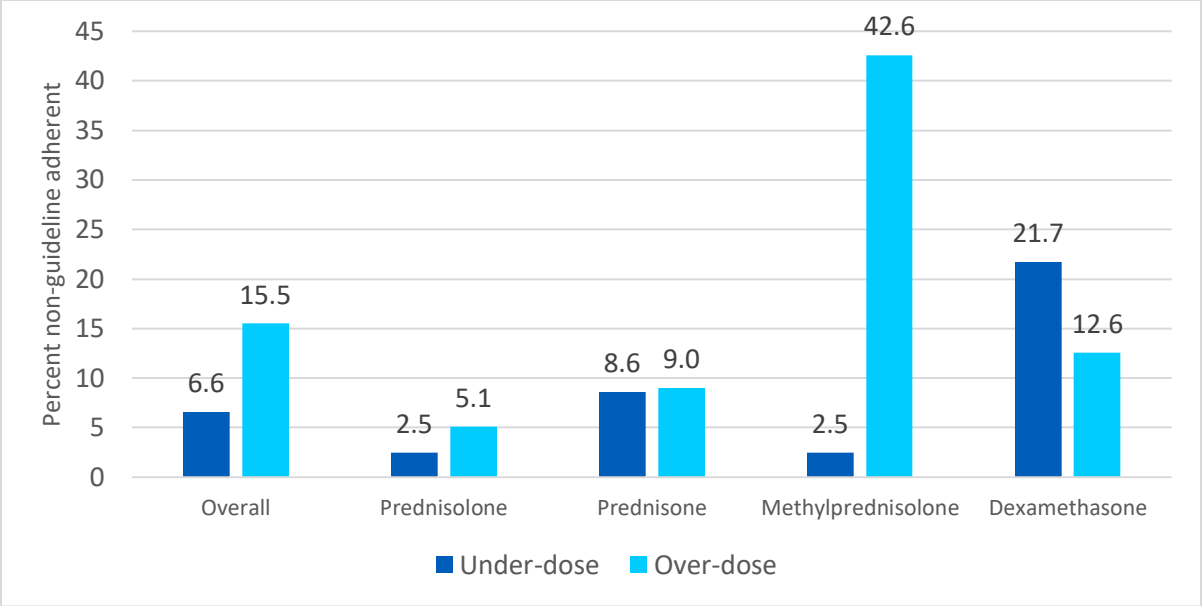

Figure 10. Proportion of prescriptions over- and under-dosed by drug

Adjusted likelihood of receiving non-guideline adherent steroid prescription

Finally, when controlling for significant demographic (age group, gender, race, insurance, and drug prescribed) and hospital-level (census region, teaching facility, and urban/rural status) factors, we found that weight status is an independent risk factor for receiving a non-guideline adherent steroid prescription during hospitalization for asthma exacerbation ($p<0.0001$). Compared to patients with a healthy weight, those with obesity had higher proportion of non-guideline adherent steroid prescriptions, with increasing likelihood as weight class increased (adjusted odds ratio 1.25 [95%CI 1.13-1.31] for class I obesity, OR 1.35 [95%CI 1.18-1.55] for class II obesity, OR 1.63 [95%CI 1.37-1.94] for class III obesity) (Figure 11).

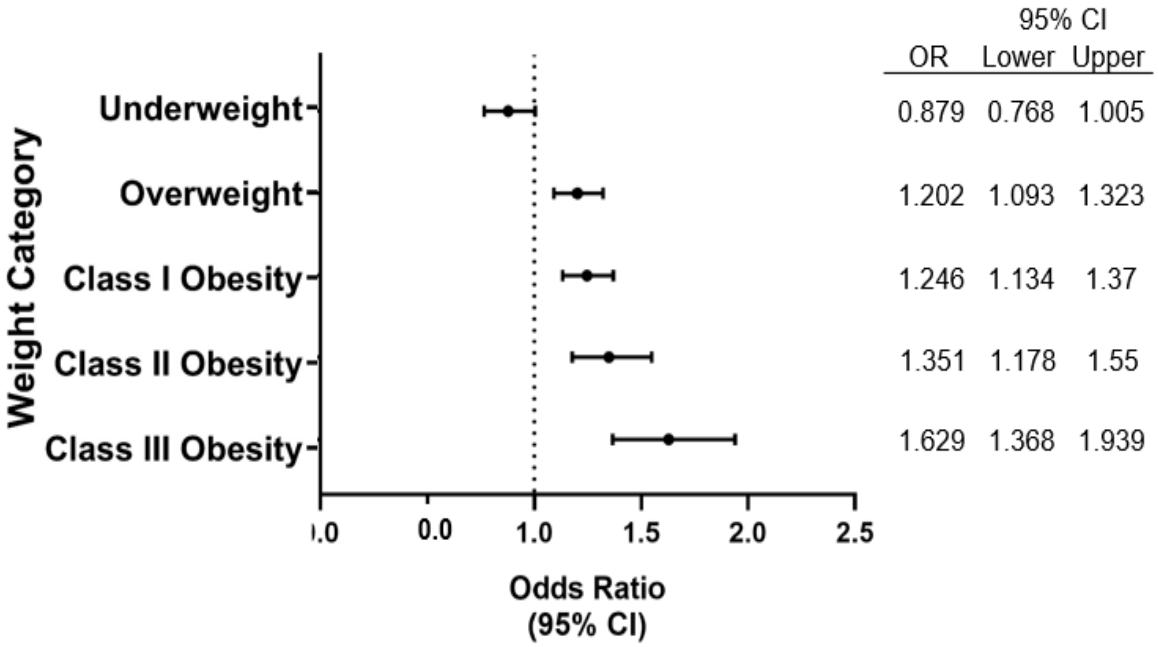

Figure 11. Adjusted likelihood of receiving non-guideline adherent steroid dose by weight category

In the adjusted model, several variables remained associated with having been prescribed a non-guideline adherent dose: dexamethasone prescription ($p<0.0001$), prednisone prescription ($p<0.0001$), methylprednisolone prescription ($p<0.0001$), age group ($p<0.0001$), race ($p<0.0001$), census region (<0.0001), whether or not the hospital was a teaching facility ($p<0.0001$), urban/rural hospital location ($p=0.0002$), and weight category ($p<0.0001$). Prescription for prednisolone, gender, and payer type were no longer significantly associated with receiving a non-guideline adherent steroid dose ($p=0.48$, 0.40, and 0.89, respectively).

CHAPTER 4

DISCUSSION

In this retrospective cohort study using the Cerner Health Facts® database of children aged 2-17 years admitted to US hospitals with asthma exacerbations in the years 2010-2017, we found that a substantial proportion of children were being prescribed non-guideline adherent steroid doses (27.8% of all encounters), and that some drugs were more likely to be over-dosed and others under-dosed. Weight category was significantly associated with likelihood of receiving non-guideline adherent steroid prescriptions; this likelihood increased as weight category increased. Many other factors were also associated with receipt of a non-guideline adherent steroid prescription, indicating that adherence to the NHLBI asthma guidelines is variable in general, not simply based on weight category.

Our findings align with and add to prior work describing increased risk of aberrant or variable prescribing practices for children with obesity.[46,50–52] One of these studies, by Gade et. al., examined variability in prescribing practices for children with obesity in an outpatient clinic setting for several commonly prescribed drugs, including prednisolone. They found specific dosing recommendations for patients with obesity for only one of the drugs they examined.[50] There was a large amount of variability in prescribing practice based on weight and the vast majority of prescribers opted to dose based on conventional TBW-based dose, or prescribed the adult maximum recommended dose for patients whose dose exceeded that amount.[50] Our results add to this work by confirming the association of receiving a non-guideline adherent steroid prescription with weight category for pediatric patients hospitalized with asthma through use of a nationally representative database with detailed patient-level data. We describe that this association is exaggerated as weight category

increases, as children with increasing degrees of obesity had higher probabilities of receiving a steroid dose outside recommended dosing guidelines.

In our adjusted model, we found that weight category remained significantly associated with receiving a non-guideline adherent steroid prescription even when adjusting for other significant patient- and hospital-level factors. The likelihood of a child with class I obesity receiving a non-guideline adherent prescription increased by about 25% compared to healthy weight children. This risk increased to over 60% for children with class III obesity. The wider confidence intervals of the ORs calculated in our adjusted model indicate a larger degree of variability in guideline adherence in children with obesity. This increasing association with weight may be because no specific dosing guidelines exist for patients with obesity.[22,31,53] This is true for the steroid drugs examined in this study, as well as the vast majority of other drugs prescribed to children with obesity.

In addition to the demonstrated association between receipt of a non-guideline adherent prescription and weight category, other factors were also associated with receiving a non-guideline adherent steroid prescription. These clinical factors included: which steroid was prescribed (dexamethasone and methylprednisolone were the most likely to be non-guideline adherent), and demographic characteristics (older children, females, African American children, and those without private insurance) were the most likely to be non-guideline adherent. Additionally, several hospital-level characteristics were also associated with receiving non-guideline adherent prescriptions: census region (encounters in the West were most likely to have non-guideline adherent prescriptions), non-teaching hospitals, and hospitals located in rural areas.

The associations mentioned above resulted in a large proportion of prescriptions overall to be non-guideline adherent (27.8%) despite the fact that NHLBI guidelines are well-established for 3 of the 4 included steroids (all but dexamethasone).[34] The NHLBI guideline was published in 2007, and includes recommendations for steroid dosing for children of all being treated for an asthma exacerbation. Recent studies have also examined the efficacy of dexamethasone for treatment of asthma exacerbations in hospitalized children, and recommended the dosing utilized in this study.[37,38] The implementation of guidelines for children hospitalized with asthma has been associated with improvements in hospitalization-related outcomes.[43] Our findings indicate that more work is needed to standardize prescribing practices universally.

In our study, we found that even when TBW-based guidelines that include daily maximum doses exist (like the NHLBI asthma guidelines), the odds of receiving a non-guideline adherent prescription is increased for children with higher weight categories. We observed over- and under-dosing, depending on the steroid prescribed. This likely places patients with obesity at greater risk of experiencing adverse drug events, including unwanted toxicities if overdosed (e.g. hyperglycemia, hypertension) or therapeutic failures if under-dosed (e.g. prolonged length of stay, increased risk of readmission).[30,40] These types of adverse events could convey both short and long-term negative effects, related to both hospital and utilization/cost outcomes. Specific dosing guidelines for children with obesity and asthma would give providers tools to make more consistent, safer decisions when prescribing drugs to this population of children.

Creation of more detailed drug dosing recommendations for children with obesity remains difficult due to a paucity of pharmacokinetic evidence in this population to support

evidenced-based guidelines.[29] For example, very little is known regarding steroid pharmacokinetics in general, including in healthy weight children and adults. A 1984 study by Milsap, et. al., described altered pharmacokinetic properties of prednisolone in men with obesity, finding a 20% increase in the volume of drug distribution (Vd) and elevated plasma free drug levels in obese men vs. health weight men.[41] These pharmacokinetic differences, coupled with the physiologic alterations obesity imposes on endogenous steroid production, may lead to differences in overall drug exposure and clinical response necessitating dose adjustments for patients with obesity.[41] To date, similar pharmacokinetic data is lacking in children. In children with asthma, there are known associations with obesity and poor health outcomes. Studies have described that children with obesity do not respond as well to inhaled therapies[32,54,55], leading to poor asthma control compared to healthy weight peers and more frequent exacerbations.[56] These differences in outcomes across weight categories suggest that alterations in dosing are necessary for children with obesity to achieve asthma control similar to that seen in healthy weight children. This phenomenon is likely true for a great number of drugs commonly prescribed to children with other common illnesses.[45]

Without the needed pharmacokinetic data to create evidenced-based dosing guidelines for children with obesity, providers must make decisions based on other available opinions. The Journal of Pediatric Pharmacology and Therapeutics has published a position statement from the Pediatric Pharmacy Advocacy Group in 2017.[53] The authors acknowledge the physiologic alterations and pharmacokinetic differences that may exist for children with obesity, but recommend that prescribers should follow TBW-based dosing in pediatric patients who weigh <40 kg, and that TBW-based dosing be used for patients > 40 kg unless the recommended adult dose for the specific indication is exceeded.[53] Others have attempted

to define more detailed, drug-specific recommendations for dosing algorithms based on anthropometric measures other than TBW (e.g. lean body weight, ideal body weight). For instance, Ross et. al. created dosing recommendations for more than 100 commonly prescribed drugs for patients in the pediatric intensive care unit based on known pharmacokinetic properties of each drug and any available pharmacokinetic data from prior study. In their study, it is recommended that dexamethasone, prednisolone and prednisone be dosed based on an individuals' TBW. In contrast, they recommended methylprednisolone be dosed based on ideal body weight due to prior evidence suggesting significantly diminished clearance rates in individuals with obesity.[45] At this time, due to lack of necessary information to formulate drug dosing guidelines for children with obesity, it is likely advisable for providers to adhere to current NHLBI guidelines for children of all weight categories.

The results of our study highlight the need for more research in this area to further elucidate the true rates of potential adverse events that may be occurring in patients with obesity, and any associated negative outcomes or increased cost. Further pharmacokinetic study of drugs in children with obesity is also imperative to ultimately make drug and disease specific dosing recommendations for this special population. Additionally, study of possible sequelae of under-dosing (e.g. treatment failure, prolonged length of stay) would be necessary as a balancing measure before uniformly recommending dosing based on TBW with a daily maximum dose as is recommended by the NHLBI and Pediatric Pharmacy Advocacy Group.[34,53]

This study should be viewed in light of several limitations. Firstly, while the Health Facts® database provides a wealth of patient-level information not available in many other

large datasets, this type of data source has some distinct problems. The data collected is often incomplete or listed in inconsistent data fields between hospitals or even units within hospitals. We believe the quality of the data included in our analysis is sound based on similarities to other published works using nationally representative samples of hospitalized children. Additionally, anthropometric data (i.e. weight, height, BMI) are often incompletely recorded during hospitalizations. Of the initial group of patients hospitalized with asthma exacerbation in the study years, approximately 21% were lost during data cleaning due to lack of complete anthropometric data. This may lead to some degree of bias within our analyzed sample. However, the use of actual measured anthropometric measures is a unique advantage of the Cerner Health Facts® database. Other commonly used datasets contain only coding information for obesity, which is notoriously poor.[23,57] From a demographic standpoint, we have some concern over the racial makeup of our included cohort. Primarily, there were very few individuals identified as Hispanic (only 2.8% of our cohort), which is substantially lower than expected based on other publications studying children hospitalized with asthma. This is an issue through the whole of the Health Facts® database. A limitation in our analysis was the inability to adequately control for asthma illness severity using the data collected from Health Facts®. Many other datasets contain illness severity information based on APR-DRG subclasses. Illness severity may play a role in the degree of steroid dosing variability and non-guideline adherent prescription rates, as sicker patients may be more likely to receive larger steroid doses above the NHLBI recommended guidelines. Lastly, there may be some limitations to how we defined non-guideline adherent drug dosing, as the definitions are rigid and do not allow for institutional- and provider-level practice variation that may be appropriate, but different from the NHLBI guidelines.

Conclusions:

Weight category is associated with receipt of non-guideline adherent steroid prescriptions for patients hospitalized with asthma exacerbation. This association increases with increasing weight category, disproportionately affecting children with severe obesity. Other patient- and hospital-level characteristics are also associated with receiving non-guideline adherent steroid prescriptions. Future studies should attempt to address differences in hospital clinical and utilization outcomes between patients with and without obesity based on drug dosing differences.

REFERENCES

1. Skinner AC, Ravanbakht SN, Skelton JA, Perrin EM, Armstrong SC. Prevalence of Obesity and Severe Obesity in US Children, 1999–2016. *Pediatrics*. February 2018:e20173459. doi:10.1542/peds.2017-3459

2. Ogden CL, Carroll MD, Lawman HG, et al. Trends in Obesity Prevalence Among Children and Adolescents in the United States, 1988-1994 Through 2013-2014. *JAMA*. 2016;315(21):2292-2299. doi:10.1001/jama.2016.6361

3. Kuczmarski RJ, Ogden CL, Guo SS, et al. 2000 CDC Growth Charts for the United States: methods and development. *Vital Health Stat 11*. 2002;(246):1-190.

4. Gulati AK, Kaplan DW, Daniels SR. Clinical Tracking of Severely Obese Children: A New Growth Chart. *Pediatrics*. 2012;130(6):1136-1140. doi:10.1542/peds.2012-0596

5. Flegal KM, Wei R, Ogden CL, Freedman DS, Johnson CL, Curtin LR. Characterizing extreme values of body mass index-for-age by using the 2000 Centers for Disease Control and Prevention growth charts. *Am J Clin Nutr*. 2009;90(5):1314-1320. doi:10.3945/ajcn.2009.28335

6. Skinner AC, Perrin EM, Moss LA, Skelton JA. Cardiometabolic Risks and Severity of Obesity in Children and Young Adults. *N Engl J Med*. 2015;373(14):1307-1317. doi:10.1056/NEJMoa1502821

7. Sorof JM, Lai D, Turner J, Poffenbarger T, Portman RJ. Overweight, ethnicity, and the prevalence of hypertension in school-aged children. *Pediatrics*. 2004;113(3 Pt 1):475-482.

8. Estrada E, Eneli I, Hampl S, et al. Children's Hospital Association consensus statements for comorbidities of childhood obesity. *Child Obes Print*. 2014;10(4):304-317. doi:10.1089/chi.2013.0120

9. Collaborators TG 2015 O. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. *N Engl J Med*. 2017;377(1):13-27. doi:10.1056/NEJMoa1614362

10. McCartney CR, Marshall JC. Polycystic Ovary Syndrome. *N Engl J Med*. 2016;375(1):54-64. doi:10.1056/NEJMcp1514916

11. Lavin JM, Shah RK. Postoperative complications in obese children undergoing adenotonsillectomy. *Int J Pediatr Otorhinolaryngol*. 2015;79(10):1732-1735. doi:10.1016/j.ijporl.2015.07.038

12. Redline S, Tishler PV, Schluchter M, Aylor J, Clark K, Graham G. Risk factors for sleep-disordered breathing in children. Associations with obesity, race, and respiratory

problems. *Am J Respir Crit Care Med*. 1999;159(5 Pt 1):1527-1532. doi:10.1164/ajrccm.159.5.9809079

13. Stokes S, Breheny P, Radulescu A, Radulescu VC. Impact of obesity on the risk of venous thromboembolism in an inpatient pediatric population. *Pediatr Hematol Oncol*. 2014;31(5):475-480. doi:10.3109/08880018.2014.886315

14. Taylor ED, Theim KR, Mirch MC, et al. Orthopedic complications of overweight in children and adolescents. *Pediatrics*. 2006;117(6):2167-2174. doi:10.1542/peds.2005-1832

15. Serdula MK, Ivery D, Coates RJ, Freedman DS, Williamson DF, Byers T. Do obese children become obese adults? A review of the literature. *Prev Med*. 1993;22(2):167-177. doi:10.1006/pmed.1993.1014

16. Reilly JJ, Methven E, McDowell ZC, et al. Health consequences of obesity. *Arch Dis Child*. 2003;88(9):748-752. doi:10.1136/adc.88.9.748

17. Hampl SE, Carroll CA, Simon SD, Sharma V. Resource utilization and expenditures for overweight and obese children. *Arch Pediatr Adolesc Med*. 2007;161(1):11-14. doi:10.1001/archpedi.161.1.11

18. Trasande L, Elbel B. The economic burden placed on healthcare systems by childhood obesity. *Expert Rev Pharmacoecon Outcomes Res*. 2012;12(1):39-45. doi:10.1586/erp.11.93

19. Trasande L, Chatterjee S. The impact of obesity on health service utilization and costs in childhood. *Obes Silver Spring Md*. 2009;17(9):1749-1754. doi:10.1038/oby.2009.67

20. Styne DM, Arslanian SA, Connor EL, et al. Pediatric Obesity—Assessment, Treatment, and Prevention: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. doi:10.1210/jc.2016-2573

21. Spear BA, Barlow SE, Ervin C, et al. Recommendations for Treatment of Child and Adolescent Overweight and Obesity. *Pediatrics*. 2007;120(Supplement 4):S254-S288. doi:10.1542/peds.2007-2329F

22. Johnson PN, Miller JL, Hagemann TM, Moffett BS. Assessment of inpatient admissions and top 25 medications for obese pediatric patients at two academic hospitals. *Am J Health-Syst Pharm AJHP Off J Am Soc Health-Syst Pharm*. 2016;73(16):1243-1249. doi:10.2146/ajhp160005

23. Katzow M, Homel P, Rhee K. Factors Associated With Documentation of Obesity in the Inpatient Setting. *Hosp Pediatr*. 2017;7(12):731-738. doi:10.1542/hpeds.2017-0100

24. Bechard LJ, Rothpletz-Puglia P, Touger-Decker R, Duggan C, Mehta NM. Influence of obesity on clinical outcomes in hospitalized children: a systematic review. *JAMA Pediatr*. 2013;167(5):476-482. doi:10.1001/jamapediatrics.2013.13

25. Maley N, Gebremariam A, Odetola F, Singer K. Influence of Obesity Diagnosis With Organ Dysfunction, Mortality, and Resource Use Among Children Hospitalized With Infection in the United States. *J Intensive Care Med*. February 2016. doi:10.1177/0885066616631325

26. Nguyen AT, Tsai C-L, Hwang L-Y, Lai D, Markham C, Patel B. Obesity and Mortality, Length of Stay and Hospital Cost among Patients with Sepsis: A Nationwide Inpatient Retrospective Cohort Study. *PloS One*. 2016;11(4):e0154599. doi:10.1371/journal.pone.0154599

27. Leyenaar JK, Ralston SL, Shieh M-S, Pekow PS, Mangione-Smith R, Lindenauer PK. Epidemiology of pediatric hospitalizations at general hospitals and freestanding children's hospitals in the United States. *J Hosp Med*. 2016;11(11):743-749. doi:10.1002/jhm.2624

28. Young KL, Demeule M, Stuhlsatz K, et al. Identification and Treatment of Obesity as a Standard of Care for All Patients in Children's Hospitals. *Pediatrics*. 2011;128(Supplement 2):S47-S50. doi:10.1542/peds.2011-0480C

29. Kendrick JG, Carr RR, Ensom MHH. Pediatric Obesity: Pharmacokinetics and Implications for Drug Dosing. *Clin Ther*. 2015;37(9):1897-1923. doi:10.1016/j.clinthera.2015.05.495

30. Harskamp-van Ginkel MW, Hill KD, Becker KC, et al. Drug Dosing and Pharmacokinetics in Children With Obesity: A Systematic Review. *JAMA Pediatr*. 2015;169(7):678-685. doi:10.1001/jamapediatrics.2015.132

31. Rowe S, Siegel D, Benjamin DK. Gaps in Drug Dosing for Obese Children: A Systematic Review of Commonly Prescribed Emergency Care Medications. *Clin Ther*. 2015;37(9):1924-1932. doi:10.1016/j.clinthera.2015.08.006

32. McGarry ME, Castellanos E, Thakur N, et al. Obesity and bronchodilator response in black and Hispanic children and adolescents with asthma. *Chest*. 2015;147(6):1591-1598. doi:10.1378/chest.14-2689

33. Carroll CL, Bhandari A, Zucker AR, Schramm CM. Childhood obesity increases duration of therapy during severe asthma exacerbations*. *Pediatr Crit Care Med*. 2006;7(6):527. doi:10.1097/01.PCC.0000243749.14555.E8

34. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. 2007:440.

35. Black MH, Zhou H, Takayanagi M, Jacobsen SJ, Koebnick C. Increased asthma risk and asthma-related health care complications associated with childhood obesity. *Am J Epidemiol*. 2013;178(7):1120-1128. doi:10.1093/aje/kwt093

36. Goleva E, Covar R, Martin RJ, Leung DYM. Corticosteroid pharmacokinetic abnormalities in overweight and obese corticosteroid resistant asthmatics. *J Allergy Clin Immunol Pract*. 2016;4(2):357-360.e2. doi:10.1016/j.jaip.2015.11.013

37. Parikh K, Hall M, Mittal V, et al. Comparative Effectiveness of Dexamethasone versus Prednisone in Children Hospitalized with Asthma. *J Pediatr*. 2015;167(3):639-644.e1. doi:10.1016/j.jpeds.2015.06.038

38. Paniagua N, Lopez R, Muñoz N, et al. Randomized Trial of Dexamethasone Versus Prednisone for Children with Acute Asthma Exacerbations. *J Pediatr*. 2017;191:190-196.e1. doi:10.1016/j.jpeds.2017.08.030

39. Keeney GE, Gray MP, Morrison AK, et al. Dexamethasone for Acute Asthma Exacerbations in Children: A Meta-analysis. *Pediatrics*. 2014;133(3):493-499. doi:10.1542/peds.2013-2273

40. Callaghan LC. Prescribing in paediatric obesity: methods to improve dosing safety in weight-based dose calculations. *Arch Dis Child - Educ Pract*. January 2018:edpract-2016-311491. doi:10.1136/archdischild-2016-311491

41. Milsap RL, Plaisance KI, Jusko WJ. Prednisolone disposition in obese men. *Clin Pharmacol Ther*. 1984;36(6):824-831.

42. Anderson WJ, Lipworth BJ. Does body mass index influence responsiveness to inhaled corticosteroids in persistent asthma? *Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol*. 2012;108(4):237-242. doi:10.1016/j.anai.2011.12.006

43. Johnson DP, Arnold DH, Gay JC, et al. Implementation and Improvement of Pediatric Asthma Guideline Improves Hospital-Based Care. *Pediatrics*. January 2018:e20171630. doi:10.1542/peds.2017-1630

44. Rutman L, Atkins RC, Migita R, et al. Modification of an Established Pediatric Asthma Pathway Improves Evidence-Based, Efficient Care. *Pediatrics*. November 2016:e20161248. doi:10.1542/peds.2016-1248

45. Ross EL, Heizer J, Mixon MA, et al. Development of recommendations for dosing of commonly prescribed medications in critically ill obese children. *Am J Health-Syst Pharm AJHP Off J Am Soc Health-Syst Pharm*. 2015;72(7):542-556. doi:10.2146/ajhp140280

46. Miller JL, Johnson PN, Harrison DL, Hagemann TM. Evaluation of inpatient admissions and potential antimicrobial and analgesic dosing errors in overweight children. *Ann Pharmacother*. 2010;44(1):35-42. doi:10.1345/aph.1M371

47. Burke CN, Voepel-Lewis T, Wagner D, et al. A retrospective description of anesthetic medication dosing in overweight and obese children. *Paediatr Anaesth*. 2014;24(8):857-862. doi:10.1111/pan.12396

48. Kaushal R, Bates DW, Landrigan C, et al. Medication errors and adverse drug events in pediatric inpatients. *JAMA*. 2001;285(16):2114-2120.

49. SAS Program (ages 0 to < 20 years) | Resources | Growth Chart Training | Nutrition | DNPAO | CDC. https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm. Published February 26, 2019. Accessed May 3, 2019.

50. Gade C, Christensen HR, Dalhoff KP, Holm JC, Holst H. Inconsistencies in dosage practice in children with overweight or obesity: A retrospective cohort study. *Pharmacol Res Perspect*. 2018;6(3):e00398. doi:10.1002/prp2.398

51. Christian-Kopp S, Sinha M, Rosenberg DI, Eisenhart AW, McDonald FW. Antibiotic dosing for acute otitis media in children: a weighty issue. *Pediatr Emerg Care*. 2010;26(1):19-25. doi:10.1097/PEC.0b013e3181cbeb00

52. Kuhle S, Fung C, Veugelers PJ. Medication use in normal weight and overweight children in a nationally representative sample of Canadian children. *Arch Dis Child*. 2012;97(9):842-847. doi:10.1136/archdischild-2011-301195

53. Matson KL, Horton ER, Capino AC, Advocacy Committee for the Pediatric Pharmacy Advocacy Group. Medication Dosage in Overweight and Obese Children. *J Pediatr Pharmacol Ther JPPT Off J PPAG*. 2017;22(1):81-83. doi:10.5863/1551-6776-22.1.81

54. Lang JE. Obesity and asthma in children: current and future therapeutic options. *Paediatr Drugs*. 2014;16(3):179-188. doi:10.1007/s40272-014-0069-1

55. Savas M, Wester VL, Staufenbiel SM, et al. Systematic Evaluation of Corticosteroid Use in Obese and Non-obese Individuals: A Multi-cohort Study. *Int J Med Sci*. 2017;14(7):615-621. doi:10.7150/ijms.19213

56. Quinto KB, Zuraw BL, Poon K-YT, Chen W, Schatz M, Christiansen SC. The association of obesity and asthma severity and control in children. *J Allergy Clin Immunol*. 2011;128(5):964-969. doi:10.1016/j.jaci.2011.06.031

57. Woo JG, Zeller MH, Wilson K, Inge T. Obesity identified by discharge ICD-9 codes underestimates the true prevalence of obesity in hospitalized children. *J Pediatr*. 2009;154(3):327-331. doi:10.1016/j.jpeds.2008.09.022

VITA

Kathryn E. Kyler was born and raised in Omaha, Nebraska. She graduated from Ralston High School in Ralston, NE, in 2004. She attended the University of Nebraska-Lincoln from 2004-2008, obtaining her undergraduate degree in Nutrition, Exercise, and Health Sciences. Following her undergraduate education, she went on to obtain her M.D. from the University of Nebraska Medical Center in Omaha, NE in 2013.

Following completion of her medical education, Dr. Kyler moved to Chicago, IL, for her pediatrics residency training at Ann and Robert H. Lurie Children's Hospital/McGaw Medical Center of Northwestern University. She successfully completed this training in 2016, and went on to continue her training with a subspecialty fellowship in Pediatric Hospital Medicine at Children's Mercy Hospital in Kansas City, MO. During her time in fellowship, she pursued a Master of Science degree in Bioinformatics with an emphasis in Clinical Research from the University of Missouri-Kansas City. Following completion of her fellowship training and master's degree in the spring of 2019, Dr. Kyler will be staying on as an assistant professor in the Division of Hospital Medicine at Children's Mercy Hospital.

Throughout her education and training, Dr. Kyler has fostered an interest in research regarding children with obesity, now particularly focused on the safety and equity of care provided to hospitalized children with obesity. Her research has resulted in several publications and one grant award to date. She plans to continue this research through her career as a clinician researcher.