EVALUATION OF THE ROLE OF ADJUNCTIVE CORTICOSTEROIDS IN THE MANAGEMENT OF CHILDREN HOSPITALIZED WITH ORBITAL CELLULITIS

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ABSTRACT

Purpose/Objectives

Orbital cellulitis is an infection of the orbit that can lead to rare, but life-altering complications. Previous studies have suggested that corticosteroids may improve recovery in patients with orbital cellulitis. However, no large, multicenter studies have examined the use of systemic corticosteroids in children with orbital cellulitis. The objectives of this current study are to describe systemic corticosteroid use and associated outcomes in a national cohort of children hospitalized with orbital cellulitis.

Design/Methods

Using the Pediatric Health Information System, we performed a retrospective cohort analysis of children aged 2 months to 18 years old hospitalized with orbital cellulitis from 2007 to 2014. Propensity score matching was performed to match children with orbital cellulitis who did or did not receive systemic corticosteroids on relevant clinical and demographic factors. Post-propensity score comparisons were performed using generalized

linear mixed-effects or conditional logistic regression modeling to assess for differences in outcomes including length of stay (LOS), cost, intensive care unit (ICU) transfer, emergency department (ED) revisits, and hospital readmissions between children who did or did not receive corticosteroids.

Results

Of 2,963 children hospitalized with orbital cellulitis who met inclusion criteria, 587 (19.8 %) received systemic corticosteroids. In the matched cohort, there were 1,072 children (536 pairs) representing 41 hospitals. In the matched cohort, the LOS (Adjusted Rate Ratio (95 % CI): 1.08 (0.95-1.22), p=0.265) were similar but the costs were higher (1.21 (1.06-1.37), p=0.004) in children who received corticosteroids compared with those who did not receive corticosteroids. Although not statistically significant, we observed a trend of higher rates of 14- and 30-day readmissions among children receiving corticosteroids compared to children who did not receive corticosteroids.

Conclusions

In this large multicenter study, children with orbital cellulitis who received systemic corticosteroids had higher costs, but similar LOS. Additionally, we observed a trend toward increased rates of readmissions among children who received systemic corticosteroids. Our findings suggest that systemic corticosteroids may not significantly improve recovery in children with orbital cellulitis. Future prospective studies are needed to more fully assess the risks and benefits of utilizing systemic corticosteroids in the management of children with orbital cellulitis.

APPROVAL PAGE

The faculty listed below, appointed by the Dean of the School of Medicine have examined a thesis titled, "Evaluation of the Role of Adjunctive Corticosteroids in the Management of Children Hospitalized with Orbital Cellulitis," presented by Jessica L. Markham, candidate for the Master of Science degree, and certify that in their opinion it is worthy of acceptance.

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CHAPTER 1

INTRODUCTION

Orbital cellulitis is an infection involving the orbital tissues that frequently develops as a complication of an acute bacterial sinusitis.[1] Due to the complex anatomy of the orbit and its proximity to and connection with the central nervous system, delayed treatment or inadequate treatment of these infections can result in significant complications, including the development of local abscess, reduced ocular motility, vision impairment, intracranial extension, and even death.[1–3] Consequently, orbital cellulitis infections remain of high concern to clinicians due to the risk of developing such severe, life-altering complications.

At this time no large, multicenter studies or clinical practice guidelines have established optimal diagnostic and treatment algorithms for orbital cellulitis. A few small, single institution studies have suggested benefit of adjunctive corticosteroid administration in patients hospitalized with orbital cellulitis[4–6]; however, no large, multicenter studies have assessed the legitimacy of these findings. Consequently, further investigation is needed to more broadly recommend corticosteroid administration as adjunctive management of orbital cellulitis infections in children.

Nationally, there is a focus on improving health care delivery and patient outcomes through development and implementation of evidence-based clinical guidelines that standardize care practices.[7] This proposed study provides the opportunity to augment our current knowledge of adjunctive corticosteroid use in children hospitalized with orbital cellulitis through analysis of a large national cohort of children. The results of this current research study may inform future prospective investigations aimed at more fully assessing

the risks and benefits of systemic corticosteroid use in children hospitalized with orbital cellulitis. Additionally, the results of this current study may be used to inform future investigations aimed at evaluating the optimal timing and dosage of systemic corticosteroids in the management of orbital cellulitis.

CHAPTER 2

REVIEW OF THE LITERAURE

Background

Orbital cellulitis is a bacterial infection that develops within the orbital tissues posterior to the orbital septum. Although it is not as common as other childhood infections (e.g., pneumonia), orbital cellulitis warrants special attention secondary to the risk for the development of serious complications including intracranial extension (e.g., meningitis and intracranial abscess), cavernous sinus thrombosis, impaired ocular motility, vision loss, and death.[1–3] The diagnosis and timely initiation of treatment of orbital cellulitis is imperative to improve patient outcomes and to prevent these serious complications.

Epidemiology

Based upon weighted national estimates from the 2012 Healthcare Cost and Utilization Project (HCUP) National Inpatient Sample, it is estimated that orbital cellulitis accounts for approximately 6,400 hospitalizations per year across all ages and an estimated 2,400 pediatric hospitalizations per year in the United States (US).[8] Despite the relative infrequency of orbital cellulitis infections, hospitalizations for orbital cellulitis are responsible for estimated national costs on the scale of $42.3 million dollars per year.[8] Although orbital cellulitis infections are observed across the age continuum, these infections are more prevalent among pediatric patients, with a mean reported age of 7.5 years.[1,9] Orbital cellulitis infections have also been reported with increased frequency among males and among patients presenting during the fall and winter seasons.[1]

Etiology and Pathogenesis

Understanding the complexity of the orbit and its structural relationship to the sinuses is important, as orbital cellulitis frequently develops following posterior extension of an adjacent bacterial sinusitis.[1,10] Specifically, the orbit is comprised of seven individual bones that became adjoined during development of the orbit, including the frontal, sphenoid, palatine, zygomatic, lacrimal, ethmoid, and maxillary bones. Among these seven bones, the ethmoid bone is of particular interest, as it lines the medial portion of the orbit, and is comprised of a paper-thin portion referred to as the lamina papyracea. The lamina papyracea is a highly-perforated portion of bone. The perforations in this bone serve an important role in the pathogenesis of orbital cellulitis by providing a direct connection from the sinuses to the orbit, allowing for bacterial translocation from an adjacent sinusitis.[1,11] Due to the frequency of orbital cellulitis infections developing secondary to bacterial sinusitis, these infections have been incorporated into the Chandler Classification[11], which describes the orbital complications of bacterial sinusitis.

In addition to its complex skeletal structure, the orbit and orbital contents are supported by a unique vascular network. In particular, the orbit and orbital contents are supported by multiple vessels that enter the orbit through three foramina, or openings, located between the bones of the orbit. The location of these vessels within the orbit not only contributes to the pathogenesis of these infections, but also contributes to the sequelae of orbital cellulitis infections. Among these vessels, the complex venous network is of particular importance in the pathogenesis of orbital cellulitis, as its valveless network can contribute to stasis and retrograde spread of bacteria.[1,11]

While the majority of orbital cellulitis infections develop as a complication of acute bacterial sinusitis, there are other possible etiologies that are important to acknowledge. In particular, orbital cellulitis has been reported following trauma to the orbit, as a complication secondary to surgical intervention to the orbit, and as a complication secondary to other bacterial infections (i.e., ophthalmic, dental, otolaryngologic, skin and soft tissue).[1] Regardless of the underlying etiology, however, the definitive diagnosis and management of these infections are largely similar.

Historically, a substantial proportion of orbital cellulitis infections were attributed to two bacterial etiologies: *Haemophilus influenzae* B and *Streptococcus pneumoniae*. However, with the recommendation for universal vaccination against these bacteria, we have seen a sharp decline in these organisms as the causative etiology.[1] Presently, the vast majority of orbital cellulitis infections, similar to bacterial sinusitis, are polymicrobial.[1] The most commonly isolated bacteria include streptococci (including *Streptococcus anginosus*, Group A β-hemolytic streptococci, and *Streptococcus pneumonia*e), *Staphylococcus aureus* species (including Methicillin-sensitive *Staphylococcus aureus* and Methicillin-resistant *Staphylococcus aureus*), non-typeable *Haemophilus influenzae*, *Moraxella catarrhalis,* and anaerobic bacteria.[1,12] Irrespective of the underlying bacterial etiology, previous studies have demonstrated that inoculation of microbes within the orbital tissues triggers the release of a number of cytokines that in turn generate an inflammatory cascade that leads to the extensive orbital edema observed in patients with orbital cellulitis.[13,14] Notably, as with other inflammatory states, cytokines IL-1, IL-6, and TNF have been observed in patients with orbital cellulitis.[13,15]

Clinical Presentation and Diagnosis

In addition to extensive orbital edema, children with orbital cellulitis frequently present with proptosis, chemosis, ophthalmoplegia, and decreased visual acuity, which are cardinal features distinguishing an orbital cellulitis infection from a less severe preseptal cellulitis infection.[1,9] Although these cardinal clinical features are important to recognize, their identification may be technically difficult to assess in children secondary to limitations in the ability of pediatric patients to effectively communicate symptoms (e.g., vision changes) and limitations in physical examination due to age and cooperativity of the child.

As clinical diagnosis may be technically limited, and as complications from orbital cellulitis may not be recognized on the basis of physical examination alone, diagnostic imaging is frequently utilized to guide medical management and to determine the need for surgical intervention for this subset of infections. Additionally, as there may be clinical overlap with other disease processes (e.g., preseptal cellultis, allergic reactions), diagnostic imaging offers the advantage of assessing for post-septal infection, which may be difficult to determine based solely on history and physical examination. Several diagnostic imaging modalities are currently available to assist with the diagnosis of orbital cellulitis, including ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI). While the choice of diagnostic imaging type is dependent on provider preference and availability, CT imaging is the most frequently utilized modality.

Management

Orbital cellulitis infections are generally managed with a course of antibiotics with surgical intervention reserved for individuals with drainable abscesses or severe disease. No

national guidelines exist in the United States, nor have any clinical trials been conducted to establish optimal empiric antibiotic regimens for this subset of infections. Similarly, there have been no clinical trials or large, multicenter studies to guide clinicians in the initiation of adjunctive therapies including systemic corticosteroid administration. While there is some evidence to suggest that surgical intervention is necessary following the development of large abscesses; there is limited evidence to guide when surgical intervention is indicated in patients with no definitive abscess collection or failure to improve with systemic antibiotic therapy alone.[1]

In a prior investigation of resource use in orbital cellulitis, we observed significant variation across hospitals in diagnostic test use, systemic corticosteroid use, and empiric antimicrobial use in children hospitalized with orbital cellulitis.[16] Within our study, we observed that nearly 20% of children were exposed to systemic corticosteroids.[16] Additionally, we observed that increased hospital-level resource utilization was associated with increased LOS without differences in ED return visits or readmissions.[16] As there are no specific guidelines to direct the clinician in the management of orbital cellulitis, there is also likely variation within and across hospitals with regards to antimicrobial duration, use of adjunctive therapies, and determination of need for and timing of surgical intervention. In other serious infections of childhood, variation in care is associated with worsened health outcomes and higher costs.[17–19] Consequently, understanding the degree of variation and uncertainty that exists in the management of orbital cellulitis infections is necessary to effectively prioritize evidence-based guideline development to improve the quality of care delivered to children with these infections.

Corticosteroid Use in the Management of Infectious Diseases

Corticosteroids are a diverse class of medications that have a wide variety of applications based on their anti-inflammatory, metabolic, anti-proliferative, and vasoconstrictive properties. However, in addition to their diverse therapeutic properties this class of medications is associated with numerous adverse effects, including neuropsychiatric (e.g., behavior changes, sleep disturbance), cardiovascular (e.g., hypertension), endocrinological (e.g., hyperglycemia, insulin resistance), musculoskeletal (e.g., osteoporosis, muscular wasting), ocular (e.g., retinopathy, cataract development), and immunosuppressive. Due to the numerous adverse effects that may be observed with this class of medications, clinicians frequently attempt to leverage their beneficial properties and limit the risk of adverse effects through administration of short-course, high-dose 'steroid bursts.' However, even with a limited course of corticosteroids, children may exhibit behavioral changes, sleep disturbance, hypertension, and hyperglycemia.

Although corticosteroids are not prescribed for many infectious processes due to concern for depression of the host's immune response and theoretical risk of masking disease progression, prior research has defined a role for these medications in certain subsets of infections including sepsis, bacterial meningitis, severe community acquired pneumonia, PCP pneumonia, croup, septic arthritis, and acute bacterial sinusitis.[20–25] In the setting of bacterial meningitis, studies have suggested that the benefit of corticosteroids is dependent on the infectious organism identified, with increased benefit noted in individuals with bacterial meningitis secondary to *Streptococcus pneumoniae*.[22] Conversely, in the setting of acute bacterial sinusitis, several studies have demonstrated that the efficacy of corticosteroids is not dependent on a particular microorganism, but rather in its role in reducing the degree

of mucosal edema and nasal drainage.[20,21] Clearly, corticosteroids are a diverse class of pharmacologic agents with a wide variety of clinical applications and mechanisms of action, even among individuals with underlying infectious processes.

Corticosteroid Use in the Management of Orbital Cellulitis

Over the last decade, several case reports and single institution studies from around the world have suggested that co-administration of corticosteroids may be beneficial in the management of orbital cellulitis infections. These studies have suggested that adjunctive corticosteroids augment pain management and time to recovery, without adversely affecting clinical outcomes when given to patients with orbital cellulitis.[4–6] In 2005, Yen et al. published a study which assessed the effect of concurrent intravenous corticosteroid administration in the management of pediatric orbital cellulitis and subperiosteal abscess.[4] In this benchmark study, 23 patients were identified (12 patients in the treatment group, 11 in the control group) based upon retrospective chart review. Outcomes analyzed in this study included length of hospital stay, need for surgical drainage, treatment course, and clinical outcomes. Although this study had several potential limitations including lack of treatment standardization, small sample size, and potential selection bias, this study demonstrated no significant adverse clinical outcomes with co-administration of corticosteroids, and additionally suggested a trend toward decreased length of hospital stay in the management of patients with orbital cellulitis and subperiosteal abscess.[4]

Two subsequent studies have also provided further evidence of the potential safety and benefits of corticosteroid administration in patients with orbital cellulitis. The first study published in 2013 by Pushker et al. demonstrated that adjunctive oral corticosteroid

administration was associated with faster resolution of inflammation with low risk or worsening infection in patients hospitalized at a tertiary eye care center in India.[5] This study was limited in its generalizability to hospitalized children in the US based on the small sample size (N=21), age distribution of the study population (age range, 11-59), later time of presentation (Mean 7.4 ± 2.8 days within the control group, and 7.9 ± 5.1 days within the corticosteroid group), and longer lengths of stay (Mean 18.4 ± 5.9 days within the control group, and 14.1 ± 3.7 days within the corticosteroid group) compared to hospitalized children in the US.[5] The second study published in 2015 by Davies et al. sought to evaluate the benefit and safety of corticosteroids, and to assess whether C-reactive protein (CRP) levels could serve as a marker for steroid initiation.[6] This study observed that children who were started on a 7-day course of corticosteroid when CRP levels were less than 4mg/dl had shorter lengths of stay (Mean 3.96 days) compared to those who did not receive corticosteroids (Mean 7.17 days).[6] Taken together, these three studies suggest a potential benefit to systemic corticosteroid administration in patients with orbital cellulitis.

The development of evidence-based practice guidelines is important to help improve health care delivery and reduce unnecessary medical costs. As discussed previously, no large clinical trials or clinical practice guidelines have defined optimal diagnostic and treatment algorithms for the management of orbital cellulitis. Although a few small, single institution studies have investigated adjunctive corticosteroid administration for orbital cellulitis, there are currently no large, multicenter studies that have assessed the role of adjunctive corticosteroids in the management of these infections. Additionally, the studies that have been published are limited in their application based on sample characteristics and size, lack of treatment standardization in some studies, and potential introduction of bias in others.

Given the risks of severe life-altering complications, high costs, and lack of strong evidence to recommend adjunctive corticosteroid use, we performed a retrospective cohort study to investigate corticosteroid use in children hospitalized with orbital cellulitis. The objectives of this current study were to describe corticosteroid use in a national cohort of children with orbital cellulitis and to determine the association between adjunctive corticosteroid use and outcomes including hospital length of stay (LOS), cost, ICU transfers, emergency department (ED) revisits, and hospital readmissions. The research questions we sought to address in our study included:

1. Is there an association between adjunctive corticosteroid administration and length of stay (LOS) in children hospitalized with orbital cellulitis?
2. Is there an association between adjunctive corticosteroid administration and cost in children hospitalized with orbital cellulitis?
3. Is adjunctive corticosteroid administration associated with increased frequency of ICU transfer in children hospitalized with orbital cellulitis?
4. Is adjunctive corticosteroid administration associated with increased frequency of 30-day emergency department ED revisits or hospital readmissions in children hospitalized with orbital cellulitis?

Given the benefits of corticosteroids in the management of infections such as acute bacterial sinusitis, and the suggested benefit in orbital cellulitis, as reported in the literature, we *hypothesize* that adjunctive treatment with corticosteroids will decrease LOS and cost in children hospitalized with orbital cellulitis.

CHAPTER 3

METHODS AND MATERIALS

Study Design and Data Source

We performed a multicenter, retrospective cohort study utilizing the Pediatric Health Information System (PHIS), an administrative and billing database of health information from 46 tertiary care children's hospitals across the US that are affiliated with the Children's Hospital Association (Lenexa, KS). Participating hospitals electronically submit detailed patient data to PHIS, including patient demographics, payment information, information on each episode of care including, but not limited to, admission date, disposition, and International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes. The participating hospitals also submit data on resource use (e.g., medication use, procedures, and imaging) for individual patients during their inpatient, observation, and emergency department visits. Patient identifiers such as medical record numbers are encrypted within the PHIS database and individual patients are assigned unique patient identifiers allowing for tracking of individual patients across visits. The current study included data from a total of 42 hospitals, with 4 hospitals excluded for billing data quality concerns.

Study Population

Inclusion Criteria

Using the PHIS administrative database, we identified children aged 2 months to 18 years old admitted to a PHIS participating hospital from January 1, 2007 to December 31,

2014 with a principal diagnosis of orbital cellulitis (ICD-9-CM 376.01). Notably, the ICD-9-CM diagnosis code 376.01 encompasses a range of orbital infections including periorbital cellulitis, orbital cellulitis, orbital abscess, and subperiosteal orbital abscess. If patients had multiple visits within a thirty-day period only the first hospitalization was included.

Exclusion Criteria

To identify children with orbital cellulitis who are otherwise healthy, we excluded patients with congenital diseases, prematurity, low birth weight, nutritional deficiencies, and complex chronic conditions[26] (Appendix A). Children with underlying diagnoses that would increase the likelihood of concomitant corticosteroid administration (e.g., asthma, adrenal insufficiency, arthritis) were excluded for the potential for corticosteroids to be administered as treatment for one of these other medical diagnoses. As the ICD-9-CM diagnosis code for orbital cellulitis includes other orbital infections, we utilized a series of exclusion criteria to reduce confounding, and to reduce the number of children with periorbital (preseptal) disease, which is generally less severe and may be managed differently than post-septal infections (i.e., may be managed with oral antibiotic therapy and supportive care). Children with possible competing ophthalmologic diagnoses were excluded. Children with secondary diagnoses of intracranial abscess and trauma were excluded, as these children would be unlikely to undergo management for orbital cellulitis alone. Children who received antifungal (e.g., itraconazole) or antiviral therapy (e.g., acyclovir), as well as those who did not receive a systemic antibiotic administered within the first 2 days of hospitalization were excluded secondary to the possibility of a non-bacterial infection. Notably, as part of a previous investigation of orbital cellulitis, we conducted a manual chart review at Children's Mercy

Kansas City to assess the accuracy of our case identification strategy.[16] Of the 213 medical records that met inclusion criteria, our identification strategy was associated with a positive predictive value for orbital cellulitis with or without abscess (i.e., post-septal infection) of 75.6%.[16]

Measures

Exposure/Primary Predictor

After application of inclusion and exclusion criteria to our study population, we identified children who received corticosteroids. The corticosteroid treatment group was defined utilizing Clinical Transaction Classification (CTC) codes for enteral and parenteral formulations of four of the most commonly utilized systemic corticosteroids: dexamethasone, prednisone, prednisolone, and methylprednisolone. CTC codes are a group of PHIS derived codes that were developed to make billing data comparable across institutions in order to allow for comparisons of resource use across hospitals. Patients to be included in the control (i.e., non-corticosteroid use) group were identified using propensity score matching procedures (defined below).

Outcome Measures

The primary outcome variable of interest in our study was LOS (recorded as the number of days between admission and discharge). The data for LOS is available directly in the PHIS database and is based on hospital data derived from the date of admission and date of discharge. As previous research has demonstrated shortened recovery times in children with orbital cellulitis, we chose to examine LOS as a surrogate measure for recovery time.

In addition to LOS, we assessed additional outcome variables including cost, ICU transfers, ED revisits, and hospital readmissions in children hospitalized with orbital cellulitis. We chose to examine costs in order to assess the impact of corticosteroid treatment on health care resource use. Costs were estimated using hospital- and year- specific cost-to-charge ratios. Costs were estimated for the index admission and for the episode of care (i.e., index admissions and readmission). ICU transfers, ED revisits, and hospital readmissions were chosen to serve as surrogate outcome measures for treatment failure and/or worsened clinical outcomes. ICU transfers were measured as transfers to the ICU after admission and were identified based on the presence of compatible CTC billing charges. ED revisits and hospital readmissions were assessed at 7, 14, and 30 days from the index admission (Appendix B). These time frames were chosen in order to best capture any subsequent visits that may have occurred secondary to treatment failure, treatment-associated adverse effects (e.g. drug allergy, reaction), or medical/surgical complication (e.g. post-surgical infection). Only related cause returns were considered. Related cause returns were defined *a priori* and by consensus, as a return for orbital cellulitis or as a return for reasons that could reasonably be attributed to management of orbital cellulitis (e.g., bacteremia, fever, and diarrhea).

Covariates Used in the Propensity Score Match

Propensity score match covariates included patient demographics (age, sex, race/ethnicity, payer), season, region of the US, and case mix index (CMI). Patient demographic and clinical characteristics were chosen based on their ability to influence the decision to utilize corticosteroids. We defined age groups within our study as follows: 2 months to less than 2 years, 2-4 years, 5-9 years, 10-14 years, and 15-18 years.

Race/ethnicity was defined as non-Hispanic black, non-Hispanic white, Hispanic, Asian, or other. Payer was defined as government insurance (e.g., Medicaid), private insurance, or other. Season was defined based on the time of year at presentation and reported as spring, summer, fall, or winter. Region of the US was defined based on the location of the hospital within the United States and reported as Northeast, South, Midwest, and West. CMI in PHIS is a relative weight assigned to each discharge based on the All-Patient Refined Diagnostic Group (APR-DRG; 3M) assignment and ARP-DRG severity of illness (SOI) measure which ranges from 1 (minor) to 4 (extreme). The weights are derived by Truven Health Analytics (Ann Arbor, MI) from its nationally-representative pediatric database as the ratio of the average charge for discharges within a specific APR-DRG / SOI combination to the average charge for all discharges in the database. Consequently, CMI serves as an administrative surrogate measure for severity of illness. For simplicity of reporting and interpretation, we split the weights at the median into 2 groups: minor and major.

Covariates Used in Post-Propensity Modeling

Surgical intervention and antibiotic exposure were treated as covariates within post-propensity score modeling, as these covariates were unlikely to affect the decision for corticosteroid initiation, but may modify the effect of corticosteroid use on the outcome. Surgical intervention was defined based on the presence or absence of procedural codes for ophthalmic or sinonasal surgical procedures. Antibiotic exposure was defined as parenteral antibiotics administered during the first 2 days of hospitalization (Appendix C-D). Exposure within the first 2 days of hospitalization was chosen in order to most closely correlate with *empiric* antibiotic choice and to minimize the influence that microbiological test results may

have on choice of antibiotic, which cannot be assessed within the PHIS database. The parenteral antibiotic category was further divided into 5 categories: 1) clindamycin alone or in combination with a non β-lactam antibiotic, 2) β-lactam alone or in combination, 3) vancomycin, daptomycin, or linezolid alone or in combination, 4) clindamycin/β-lactam combinations, and 5) other antibiotic. The other antibiotic category consisted of rifampin, tetracyclines, macrolides, trimethoprim/sulfamethoxazole, nitroimidazoles, quinolones, and β-lactam antibiotics not typically prescribed for the management of orbital or sinus infection. A child's antibiotic regimen was categorized based upon the broadest spectrum of activity of the administered antibiotic agents. Categorization was reviewed and confirmed by two board-certified pediatric infectious diseases physicians in the study group.

Data Collection Procedures

Investigators queried data from the Pediatric Health Information System (PHIS) to generate a study population based on the previously described inclusion and exclusion criteria. The data within the PHIS database is de-identified and data was recorded only for those records meeting all inclusion/exclusion criteria. Due to the de-identified nature of the data stored within PHIS and low risk for breach of confidentiality a Waiver of Informed Consent and Health Insurance Portability and Accountability Act (HIPAA) Authorization was sought during the IRB approval. The study has been reviewed and approved by the Children's Mercy Kansas City Institutional Review Board (IRB) and a request to rely on Children's Mercy IRB has been completed and approved by the University of Missouri-Kansas City IRB.

Statistical Analysis

From the PHIS database, we identified all children meeting the specified inclusion and exclusion criteria. Next, we divided children based on the presence or absence of exposure to corticosteroids. Prior to matching, we utilized descriptive statistics to describe patient demographics and our pre-specified covariates for our corticosteroid and no corticosteroid groups. We utilized propensity score matching to define a cohort of individuals who did not receive corticosteroids during their admission. Propensity score matching is a statistical technique that can be used to identify a comparison group by accounting for potential confounding from baseline covariates; this technique allows for estimation of a treatment effect from observational data.[27] In our study, we used multivariable logistic regression models to generate propensity scores for exposure to corticosteroids. Variables used to generate our propensity scores included our covariates age, sex, race/ethnicity, payor, season, region of the US, and case mix index. In matching controls to cases, we utilized a greedy nearest neighbor algorithm and performed matching within hospitals. The model's calculated C-statistic was 0.73, indicating that the model provided a good prediction of treatment group assignment.

Post-propensity score comparisons among children who did or did not receive corticosteroids were made using generalized linear mixed-effects modeling for LOS and cost data or conditional logistic regression modeling for ICU transfer, ED revisit, and readmission data. Post-propensity score comparisons were adjusted for surgical intervention and antibiotic exposure. All analyses were performed with SAS version 9.2 (SAS Institute, Cary, NC), and p values <0.05 were considered statistically significant.

Sample Size Determination

Sample estimates were determined *a priori*. Given the large variation in LOS observed in prior studies, we decided to be more conservative in our sample size estimate and to use a larger value of 4 days for the standard deviation of differences (which increases the number of patients per group required to achieve 80% power). Based on prior studies, we estimated that we would need to obtain aggregate information on approximately 1010 patients (505 pairs) to detect a clinically meaningful difference in LOS, which we assume to be a difference in length of stay of 0.5 days. With a sample size of 505 pairs, we have 80% power to detect a difference in means of 0.5 days, assuming a standard deviation of differences of 4 and a two-sided significance level of 0.05. Assuming a mean cost of $6000 in one group, $6500 in the second group (estimated cost derived from the mean cost for a hospitalization for orbital cellulitis as represented in the HCUP database[8] with $500 chosen to represent the least economically significant difference in cost), and a standard deviation of $2000, we estimated that we would need to obtain aggregate information on approximately 676 patients (338 pairs) to achieve 90% power with a two-sided significance level of 0.05. Thus, with a minimum of 505 pairs, our study should be sufficiently powered to examine both LOS and cost outcomes.

Unplanned 30-day, all-condition readmission rates in children are low, occurring at an estimated rate of 6.5%.[28] As readmission rates are low for the majority of pediatric diseases, we estimate that we would be attempting to detect a small percentage difference in readmission rates. Assuming a sample size of 505 pairs, we will have approximately 20% power to detect a difference of 1% in readmission rate based on a McNemar test using a two-sided significance level of 0.05. Due to anticipated low rates of ICU transfers and ED revisits

we would similarly anticipate low power to detect differences between groups. Therefore, based on *a priori* sample size and power estimates, we anticipate that the study will be powered for LOS and cost, but we will need to interpret these other outcomes with caution.

CHAPTER 4

RESULTS

Characteristics of the Study Population

From the PHIS database, we have been able to identify a total of 5,546 hospitalized children aged 2 months to 18 years admitted with a principal ICD-9-CM code for orbital cellulitis. Following application of our exclusion criteria, there were 2,963 hospitalizations for orbital cellulitis within the study period that met inclusion criteria (Figure 1). Of the 2,963 children who met inclusion criteria, 587 (19.8%) children received systemic corticosteroids. The majority of children received dexamethasone (85.5%), with fewer children receiving prednisolone, prednisone, and methylprednisolone.

In the pre-match study population, 74.0% of children were < 10 years of age, 63.4% were male, and 52.4% were non-Hispanic white (Table 1). While the distributions of sex, race, payer, and season did not significantly differ between children who did or did not receive corticosteroids, we did observe statistically significant baseline differences in the pre-match population based on age, region of the US, and CMI. Notably, the differences in age, region of the US, and CMI that were observed provide further justification for the value of using the statistical technique of propensity score matching.

Following propensity score matching, the overall study population was 1072 (representing 41 of the 42 hospitals) with 536 children receiving systemic corticosteroids and 536 not receiving corticosteroids (Table 2). Of children who were matched, 65.6% were less than 10 years of age, 64.1% were male, 55.8% were non- Hispanic white, 59.9% were hospitalized during the spring and winter, and 68.8% were located in the West or South.

Nearly two-thirds of the post-match cohort were categorized as having a major case-mix index. The c-statistic for the propensity score model was 0.73.

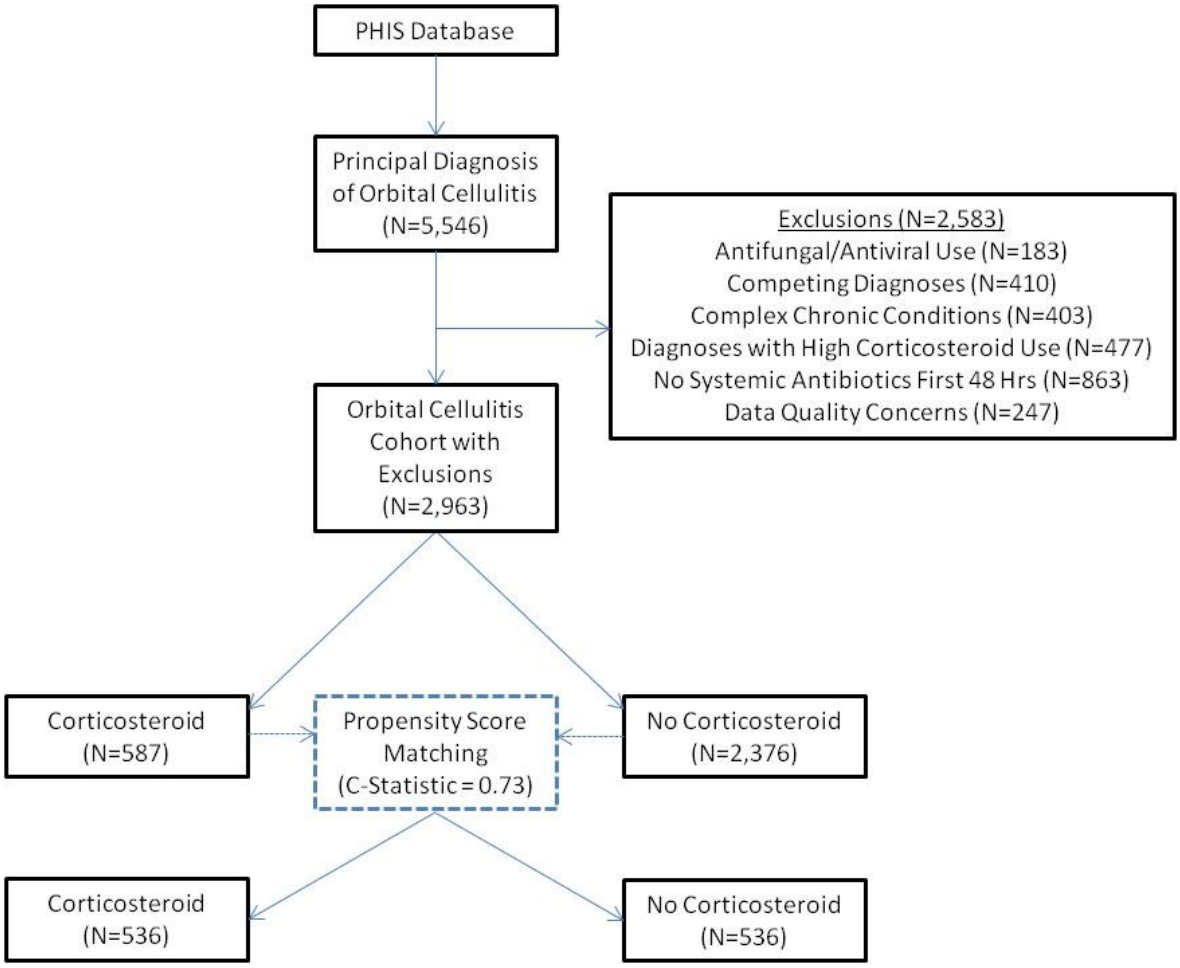


Figure 1. Study cohort flow diagram.

Table 1. Demographic and clinical characteristics of the pre-match study population by treatment group. Data are presented as number (percent).

		Overall	**No Steroids**	**Steroids**	***P***
N	---	2963	2376 (80.2)	587 (19.2)	---
Age	2 mo-1 yr	604 (20.4)	550 (23.1)	54 (9.2)	<0.001
	2-4 yr	671 (22.6)	570 (24.0)	101 (17.2)	
	5-9 yr	918 (31.0)	720 (30.3)	198 (33.7)	
	10-14 yr	619 (20.9)	422 (17.8)	197 (33.6)	
	15-18 yr	151 (5.1)	114 (4.8)	37 (6.3)	
Sex	Male	1880 (63.4)	1491 (62.8)	389 (66.3)	0.113
	Female	1083 (36.6)	885 (37.2)	198 (33.7)	
Race/Ethnicity	Non-Hispanic White	1553 (52.4)	1225 (51.6)	328 (55.9)	0.408
	Non-Hispanic Black	651 (22.0)	535 (22.5)	116 (19.8)	
	Hispanic	367 (12.4)	300 (12.6)	67 (11.4)	
	Asian	61 (2.1)	50 (2.1)	11 (1.9)	
	Other	331 (11.2)	266 (11.2)	65 (11.1)	
Payer	Government	1339 (45.2)	1093 (46.0)	246 (41.9)	0.139
	Private	1406 (47.5)	1106 (46.5)	300 (51.1)	
	Other	218 (7.4)	177 (7.4)	41 (7.0)	
Season	Spring	823 (27.8)	659 (27.7)	164 (27.9)	0.571
	Summer	595 (20.1)	473 (19.9)	122 (20.8)	
	Fall	637 (21.5)	523 (22.0)	114 (19.4)	
	Winter	908 (30.6)	721 (30.3)	187 (31.9)	
Region of the United States	Midwest	737 (24.9)	636 (26.8)	101 (17.2)	<0.001
	Northeast	500 (16.9)	430 (18.1)	70 (11.9)	
	South	1100 (37.1)	819 (34.5)	281 (47.9)	
	West	626 (21.1)	491 (20.7)	135 (23.0)	
Case-Mix Index	Minor	1755 (59.2)	1555 (65.4)	200 (34.1)	<0.001
	Major	1208 (40.8)	821 (34.6)	387 (65.9)	

Table 2. Demographic and clinical characteristics of the post-match study population by treatment group. Data are presented as number (percent). The c-statistic for the propensity score model was 0.73.

		Overall	No Steroids	Steroids	*P*
N	---	1072	536 (50.0)	536 (50.0)	---
Age	2 mo-1 yr	115 (10.7)	62 (11.6)	53 (9.9)	0.381
	2-4 yr	204 (19.0)	107 (20.0)	97 (18.1)	
	5-9 yr	384 (35.8)	198 (36.9)	186 (34.7)	
	10-14 yr	311 (29.0)	142 (26.5)	169 (31.5)	
	15-18 yr	58 (5.4)	27 (5.0)	31 (5.8)	
Sex	Male	687 (64.1)	335 (62.5)	352 (65.7)	0.279
	Female	385 (35.9)	201 (37.5)	184 (34.3)	
Race/Ethnicity	Non-Hispanic White	598 (55.8)	308 (57.5)	290 (54.1)	0.667
	Non-Hispanic Black	203 (18.9)	96 (17.9)	107 (20.0)	
	Hispanic	133 (12.4)	69 (12.9)	64 (11.9)	
	Asian	20 (1.9)	9 (1.7)	11 (2.1)	
	Other	118 (11.0)	54 (10.1)	64 (11.9)	
Payer	Government	473 (44.1)	237 (44.2)	236 (44.0)	0.912
	Private	540 (50.4)	268 (50.0)	272 (50.7)	
	Other	59 (5.5)	31 (5.8)	28 (5.2)	
Season	Spring	321 (29.9)	167 (31.2)	154 (28.7)	0.820
	Summer	210 (19.6)	104 (19.4)	106 (19.8)	
	Fall	220 (20.5)	110 (20.5)	110 (20.5)	
	Winter	321 (29.9)	155 (28.9)	166 (31.0)	
Region of the United States	Midwest	194 (18.1)	97 (18.1)	97 (18.1)	1.000
	Northeast	140 (13.1)	70 (13.1)	70 (13.1)	
	South	478 (44.6)	239 (44.6)	239 (44.6)	
	West	260 (24.3)	130 (24.3)	130 (24.3)	
Case-Mix Index	Minor	393 (36.7)	202 (37.7)	191 (35.6)	0.486
	Major	679 (63.3)	334 (62.3)	345 (64.4)	

Corticosteroid Use and Outcomes

Prior to matching, children who received corticosteroids had a statistically significantly different median LOS compared to children who did not receive corticosteroids (Table 3). Prior to matching, children who received corticosteroids also had statistically higher costs, increased rates of ICU transfer, increased ED revisit rates, and increased rates of readmissions.

Table 3. Outcomes in the pre-match study population by treatment group. Data are presented as median [interquartile range] or N (%). Differences between corticosteroid and no corticosteroid treatments groups are significant at $P<0.05$.

	Overall (n = 2963)	**No Steroids (n = 2376)**	**Steroids (n = 587)**	***P***
Length of Stay (Days)	3 [2, 4]	3 [2, 4]	4 [3, 6]	<0.001
Index Cost ($)	5218 [3321, 8980]	4663 [3076, 7639]	9347 [5551, 14602]	<0.001
Episode Cost				
7 Day	5296 [3349, 9185]	4703 [3097, 7764]	9661 [5653, 14921]	<0.001
14 Day	5309 [3350, 9236]	4716 [3100, 7783]	9750 [5653, 15019]	<0.001
30 Day	5328 [3359, 9298]	4742 [3117, 7807]	9835 [5653, 15024]	<0.001
ICU Transfer (N)	46 (1.6)	25 (1.1)	21 (3.6)	<0.001
ED Revisit				
7 Day	45 (1.5)	30 (1.3)	15 (2.6)	0.022
14 Day	65 (2.2)	43 (1.8)	22 (3.7)	0.004
30 Day	89 (3.0)	63 (2.7)	26 (4.4)	0.024
Readmission				
7 Day	43 (1.5)	25 (1.1)	18 (3.1)	<0.001
14 Day	57 (1.9)	33 (1.4)	24 (4.1)	<0.001
30 Day	69 (2.3)	43 (1.8)	26 (4.4)	<0.001

ED= emergency department; ICU= intensive care unit

In the matched cohort, the median index LOS was 4 [IQR 3, 6] days for children who received corticosteroids and 3 [IQR 2, 4] days for children who did not receive corticosteroids (Table 4). In the matched cohort, children who received corticosteroids had an average LOS that was not statistically different than that for children who did not receive corticosteroids. In the matched cohort, the median index costs were $9315 [IQR $5614, $14766] for children who received corticosteroids and $5466 [IQR $3569, $9026] for children who did not receive corticosteroids. Children who received corticosteroids had average index admission costs that were 21% higher than children who did not receive corticosteroids (p=0.004). Episode costs that included the index admission and readmission

were similarly higher at 7-, 14-, and 30-days (All p<0.001). Although not statistically significant, children with orbital cellulitis who received corticosteroids had a trend of increased rates of 14- and 30-day readmissions compared to children who did not receive systemic corticosteroids.

Table 4. Outcomes in the post-match study population by treatment group. Data are presented as median [interquartile range] or N (%). Post-match comparisons are presented as adjusted odds ratios (aOR) or adjusted rate ratios (aRR) with 95% confidence intervals (CI).

	Overall (n = 1072)	**No Steroids (n = 536)**	**Steroids (n = 536)**	**aOR or aRR (95% CI)**	***P***
Length of Stay (Days)	4[2, 5]	3 [2, 4]	4 [3, 6]	1.08 (0.95-1.22)	0.265
Index Cost ($)	7103 [4314, 12093]	5466 [3569, 9026]	9315 [5614, 14766]	1.21 (1.06-1.37)	0.004
Episode Cost ($)					
7 Day	7318 [4350, 12387]	5520 [3569, 9120]	9690 [5679, 15026]	1.24 (1.09-1.41)	0.001
14 Day	7347 [4350, 12457]	5529 [3569, 9147]	9741 [5679, 15051]	1.25 (1.10-1.42)	0.001
30 Day	7364 [4350, 12525]	5548 [3569, 9268]	9792 [5679, 15054]	1.24 (1.10-1.41)	0.001
ICU Transfer (N)	26 (2.4)	7 (1.3)	19 (3.5)	1.8 (0.5-6.9)	0.374
ED Revisit					
7 Day	25 (2.3)	8 (1.5)	17 (3.2)	2.4 (0.8-7.4)	0.124
14 Day	32 (3.0)	11 (2.1)	21 (3.9)	2.2 (0.8-6.4)	0.147
30 Day	37 (3.5)	14 (2.6)	23 (4.3)	2.1 (0.8-5.9)	0.154
Readmission					
7 Day	18 (1.7)	5 (0.9)	13 (2.4)	3.0 (0.8-11.6)	0.109
14 Day	25 (2.3)	6 (1.1)	19 (3.5)	3.0 (1.0-9.1)	0.054
30 Day	31 (2.9)	8 (1.5)	23 (4.3)	2.6 (1.0-6.7)	0.056

ED= emergency department; ICU= intensive care unit

CHAPTER 5

DISCUSSION

In this multicenter, retrospective cohort study, we found that nearly 20% of children receive systemic corticosteroids in the management of orbital cellulitis. In our study, children receiving systemic corticosteroids in the management of orbital cellulitis had similar LOS, but higher costs compared to children who did not receive corticosteroids. Although not reaching statistical significance, we observed a trend of higher rates of 14- and 30-day readmissions among children receiving corticosteroids compared to children who did not receive corticosteroids. Taken together, our results suggest that use of adjunctive systemic corticosteroids in the management of orbital cellulitis may not be as beneficial as previously reported in the literature.

Wide variation exists in the management of orbital cellulitis infections. Within our cohort, approximately 1 in 5 children received corticosteroids, with the vast majority receiving dexamethasone. The variation in systemic corticosteroid use across hospitals that we observed may reflect the absence of strong evidence for clinical benefit in treating orbital cellulitis infections, physician concern for the adverse effect profile of corticosteroids (i.e., concern for host immune suppression), or differential prescribing based on severity of illness or other clinical and demographic factors. Previous research of other pediatric conditions has demonstrated that wide variation in care is associated with higher hospitalization rates, prolonged LOS, and higher cost.[17,18,30–32] Future investigations aimed at defining best practices for orbital cellulitis infections are essential to develop evidence-based guidelines aimed at reducing unnecessary practice variation and improving patient outcomes.

Previous studies have suggested that systemic corticosteroids may be safely administered and helpful in improving recovery time in patients with orbital cellulitis; however, the generalizability of these findings to all pediatric patients is limited by their study designs, including their evaluation at single centers within small populations of varying aged patients.[4–6] In particular, use of corticosteroids was associated with decreased LOS in two studies, and with similar average LOS, but shorter median LOS in yet another study.[4–6] In our current study, we observed similar LOS among children who did or did not receive corticosteroids. Although prior studies have suggested that corticosteroids reduce orbital inflammation and consequently improve recovery times, the similar LOS observed in children who did or did not receive corticosteroids in our study, suggests that corticosteroids may not significantly impact LOS in children hospitalized with orbital cellulitis. The similar LOS that we observed may also reflect diminution of the effects of corticosteroid on LOS secondary to variability in the timing, dose, or length of corticosteroid therapy among patients- factors which we are unable to assess based on our current study design. Taken together, our findings suggest continued clinical equipoise, and they underscore the need for further prospective investigations aimed at describing the efficacy and safety of corticosteroid use in broad populations of children hospitalized with orbital cellulitis.

Costs have previously not been examined in other investigations of corticosteroid use in patients hospitalized with orbital cellulitis. In our study, children receiving corticosteroids had adjusted costs of hospitalization (with or without readmission) that were approximately 21-25% higher than children who did not receive corticosteroids. While some of the differences in cost between those who did, or did not receive corticosteroids may reflect the costs of corticosteroid administration itself, a portion of this difference may also relate to

subtle differences in study population characteristics (i.e., differences in study populations secondary to the contributions of unmeasured covariates). With the growing costs of health care, future investigations should examine if corticosteroid use in patients with orbital cellulitis is associated with not only a clinical benefit, but also whether widespread use negatively impacts the health care system (e.g., cost, readmissions).

Although not reaching statistical significance, children receiving corticosteroids in our study had a trend toward increased rates of 14- and 30-day hospital readmissions compared to those not receiving corticosteroids. Within our study, we accounted for various clinical and demographic factors including case-mix index within our propensity score match and adjusted our models for surgical intervention and antibiotic exposure. Despite our attempt to control for important clinical and demographic factors within our propensity score match, the higher frequency of ICU transfer among patients receiving corticosteroids may reflect increased risk of adverse events secondary to systemic corticosteroid prescribing or perhaps increased severity of illness. Similarly, while we observed increased frequency of readmissions among children in our cohort who received corticosteroids; these findings were not statistically significantly different and should be interpreted with caution as the current study was not powered to detect differences in readmission rates. Consequently, our findings further highlight the need for future prospective investigations to more completely describe the relationship between corticosteroid use and outcomes in children hospitalized with orbital cellulitis.

This study has several important limitations. First, the ICD-9-CM diagnosis code 376.01 encompasses a range of orbital infections including periorbital cellulitis, orbital cellulitis, orbital abscess, and subperiosteal orbital abscess. As such, there is a risk for

misclassification bias. We attempted to reduce misclassification bias through exclusion of potentially confounding secondary diagnoses, exclusion of children who did not receive antibiotics within the first 2 days of hospitalization, and use of propensity score matching to match patients based on clinical and demographic factors. While our case definition likely includes both pre- and post-septal orbital infections, the use of propensity score matching and our c-stat of 0.73 suggests that we likely achieved a good balance of covariates across our exposure groups. The similarity of our study's original cohort to previous studies[9,32-34], as well as the PPV of 75.6% that we observed through chart review[16] further supports the accuracy of our case identification strategy. Another limitation of this study is that the PHIS database contains administrative data only. Consequently, we were limited in our ability to assess how factors such as severity of illness and results of laboratory or microbiologic data may have affected clinical decision-making. We attempted to control for severity of illness in the propensity score by matching on CMI and controlling for surgical intervention and antibiotic use in post-propensity score models. Although not statistically significant, the observed difference in rates of ICU use between groups may reflect a true finding or confounding from unmeasured differences in severity of illness that were unable to be accounted for with our administrative dataset and statistical techniques. Finally, our results may not be generalizable to all pediatric patients, as our current study only included children hospitalized at freestanding, tertiary care children's hospitals, which may not fully represent all hospitalized children in the US.

CHAPTER 6

CONCLUSIONS

From our large, multicenter study of children hospitalized with orbital cellulitis we observed that children who received systemic corticosteroids did not have shorter lengths of stay, but did have higher costs. In addition, there was a trend for increased readmission rates within 14 and 30 days. Contrary to previous studies, our findings suggest that use of systemic corticosteroids in children with orbital cellulitis may not improve recovery times and may be associated with worsened clinical outcomes. Despite the negative findings in our study, future prospective investigations are needed to more decisively recommend for or against corticosteroid use in children. Future investigations might seek to further identify the risks and benefits of systemic corticosteroid use, understand population characteristics that may predict improved outcomes with corticosteroids, and investigate the optimal timing and dosage of corticosteroids for children hospitalized with orbital cellulitis.

APPENDIX A

Excluded Secondary Diagnoses

Secondary Diagnoses	**ICD-9-CM**
Complex Chronic Conditions	Feudtner *et al*[26]
Congenital Conditions	253, 740-759.9, 765.17, 765.27, V136-V136.9, V213.4-V213.5
Corticosteroids	255-255.9, 493-493.92, 714.30-714.33759.1, V586.5
Intracranial Abscess	324-324.9
Neoplasms	140-239.9, V107-108.9, V123, V153, E933.1
Nutritional Deficiency	260-269.9
Ophthalmologic Conditions	077-079.98, 360-360.9, 369, 370.49, 371-372.9, 374-375.9, 377-379.99, V124.9, V430, V457.8
Infectious Conditions (e.g., viral, fungal)	052-054.9, 098.4, 114-118, V586.2
Trauma	349.3-349.39, 733.19, 800-999, E001-E029.2, E800-E849.9, E879, E880-E927.9, E928.3, E928.8-E929.5, E960-E969, E980-E989.9, V125.2, V125.5, V155.1-V155.2, V155.9, V908.9, V541.9

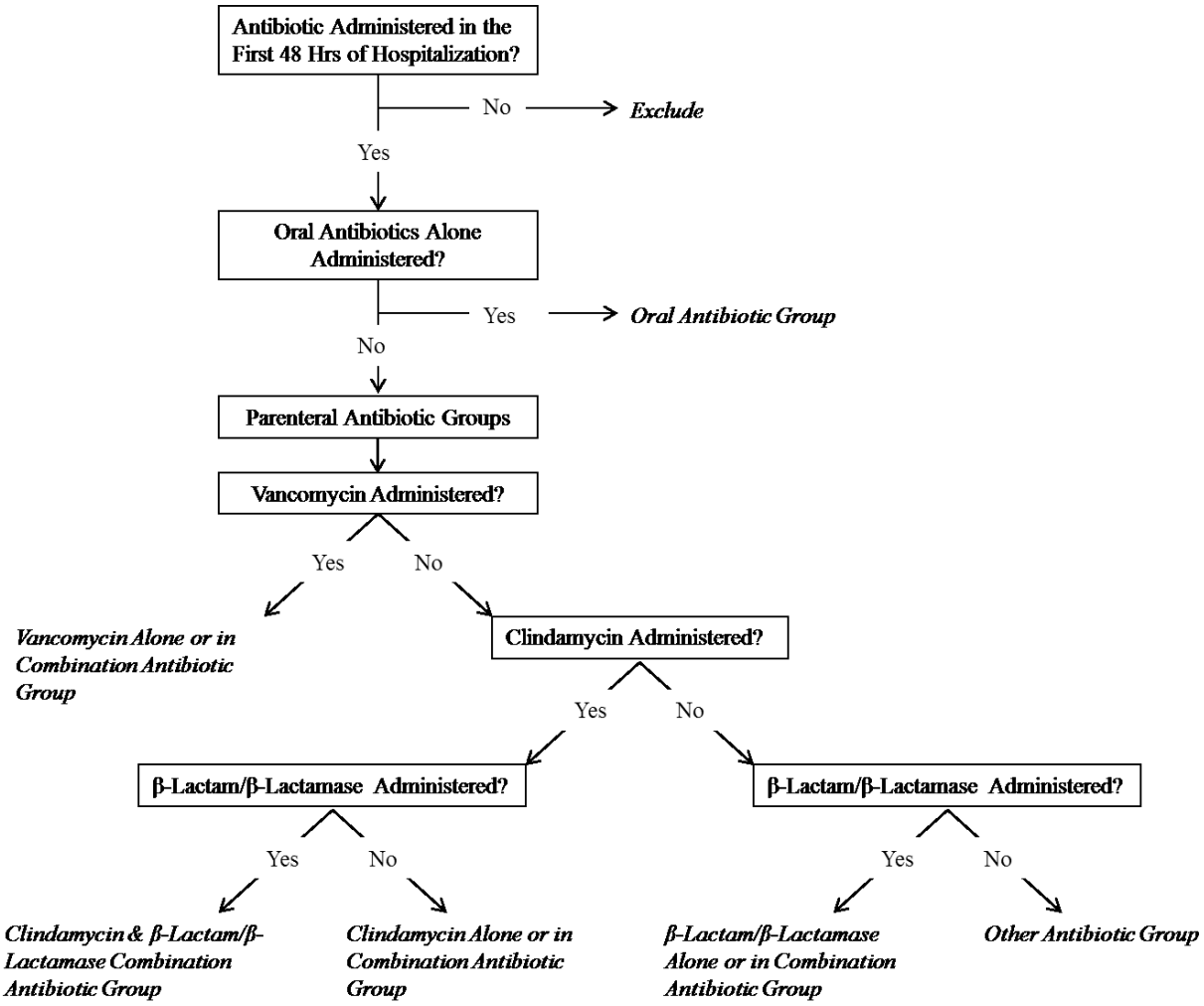
APPENDIX B

Indications for 30-Day Emergency Department (ED) Revisits and Readmissions

Type of Return	Indication for Return (ICD-9-CM)	N	%
ED Revisits	Inflammation or infection of the eye (360.0, 373.13, 376.01)	20	37.7
	Fever (780.6)	11	20.8
	Malfunction, inflammation, or infection of a device, implant, or graft (996.1, 999.31)	8	15.1
	Diarrhea or dehydration (276.51, 787.91)	4	7.5
	Headache (784.0)	3	5.7
	Sinusitis (473.2)	3	5.7
	Allergic reactions (693.0, 708.0)	2	3.8
	Cellulitis and abscess of face (682.0)	2	3.8
Readmissions	Inflammation or infection of the eye (360.0, 373.13, 374.82, 375.32, 376.01, 376.02)	37	54.4
	Allergic reactions (693.0, 708.0)	6	8.8
	Cellulitis and abscess of face (682.0)	5	7.4
	Sinusitis (461, 473)	5	7.4
	Malfunction, inflammation, or infection of a device, implant, or graft (996.1, 999.31, 999.32)	4	5.9
	Intracranial abscess, meningitis, or other intracranial infection (322.9, 324.0, 324.9)	3	4.4
	Diarrhea or dehydration (276.51, 787.91)	2	2.9
	Fever (780.6)	2	2.9
	Headache or epistaxis (784.0, 784.7)	2	2.9
	Lymphadenitis (289.3)	1	1.5
	Complications of surgical procedures or medical care (998.31)	1	1.5

APPENDIX C

Antibiotic Classification Scheme



APPENDIX D

Antibiotic Categorization Presented as Antibiotic with Clinical Transaction Code (CTC)

Antibiotic Groups	**Antibiotic (CTC)**
Clindamycin	Clindamycin (124143)
Vancomycin	Daptomycin (124129), Linezolid (124137), Vancomycin (124133)
β-Lactam/β-Lactamase	Ampicillin/Sulbactam (121231), Cefepime (122252), Cefotaxime (122211), Ceftaroline (122271), Ceftazidime (122221), Ceftizoxime (122227), Ceftriaxone (122231), Ertapenem (124113), Imipenem (124105), Meropenem (124118) Piperacillin/Tazobactam (121265), Ticarcillin/Clavulanate (121271)
Other Antibiotic	Ampicillin (121225), Azithromycin (122421), Aztreonam (124121), Cefazolin (122109), Cefuroxime (122177), Ciprofloxacin (123201), Doxycycline (123115), Levofloxacin (123215), Metronidazole (124164), Moxifloxacin (123225), Nafcillin (121247), Oxacillin (121251), Penicillin G (121207,121207), Piperacillin (121261), Rifampin (126245), Trimethoprim/Sulfamethoxazole (124451)

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VITA

Dr. Jessica Lynn Markham was born on June 14, 1985 in Pittsfield, Massachusetts. She was educated at local public schools and graduated from Taconic High School as class valedictorian in 2003. She attended Wellesley College from 2003-2007, and graduated Phi Beta Kappa and magna cum laude in 2007. Her degree was a Bachelor of Arts in Chemistry and she received Honors in Chemistry after defending her senior thesis entitled, "Using *in vivo* and *ex vivo* ^{1}H NMR spectroscopy to examine brain metabolite concentrations in a mouse model of Rett syndrome."

From 2007-2011, she attended Albany Medical College, receiving her Doctor of Medicine degree in 2011. Dr. Markham completed a Pediatric Residency at Connecticut Children's Medical Center through the University of Connecticut. She completed her pediatric residency in 2014, becoming board certified in Pediatrics later that year.

In 2014, Dr. Markham began a three-year fellowship in Pediatric Hospital Medicine at Children's Mercy Kansas City. During her fellowship, Dr. Markham began work toward a Master of Science in Bioinformatics degree. Upon completion of her fellowship and her degree requirements, Dr. Markham plans to continue her career and pursue her research interests in Pediatric Hospital Medicine as faculty of Children's Mercy Kansas City.