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ARTICLE



Analysis of medication patterns for pediatric asthma patients in emergency department: Does the sequence placement of glucocorticoids administration matter?

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ABSTRACT

Objectives: Timely glucocorticoid administration is associated with decreased admission rate and is thus a common quality metric for ED asthma care; less is known about the impact of the timing of glucocorticoids in the context of the sequence of asthma medications administered. Therefore, we investigated the distribution of asthma medication sequences in one ED and analyzed the effect of the sequence placement of glucocorticoids administration on treatment outcomes.

Methods: A retrospective study using five-year electronic health record data obtained from an academic urban children's hospital ED was conducted. We clustered the sequences of medication administration using an exact string-matching algorithm to identify the most frequently used asthma medication sequences. Then, we used the identified patterns to perform statistical tests to examine the effect of the sequence placement of glucocorticoids administration on the outcomes length-of-stay and ED disposition.

Results: A total of 4,844 encounters were included in our study. The ten most common treatment sequences accounted for 43% of all encounters. Stratified analyses confirmed that treatment sequences pattern was correlated with patient severity, but ED crowding does not impact treatment sequences. In multivariable models, glucocorticoids administration earlier in the treatment sequence was associated with shorter length of stay and lower hospital admission rates.

Conclusions: By analyzing medication sequence patterns for the ED encounter of pediatric asthma, we found that the earlier sequence placement of glucocorticoids administration is associated with improved outcomes. Our findings can help inform quality improvement and clinical guideline development related to ED asthma care for children.

ARTICLE HISTORY

KEYWORDS

Emergency department; exact-string matching algorithm; pediatric asthma; timely healthcare delivery; treatment sequences

Introduction

Among United States children, asthma is common—affecting 8.3% of children (1)—and costly: asthma is the third leading cause of hospitalization among children younger than 15 and the leading cause of missed school days in the United States (2). Emergency departments (EDs) play an important role in providing medical care for children with acute asthma exacerbations, with over 700,000 ED asthma-related visits per year in the US, representing 3.4% of all ED visits by children (3–7). Approximately 76% of childhood asthma admissions are determined by ED providers (8–10). Most of the costs incurred occur during asthma exacerbations;

optimizing the quality of care for exacerbations may reduce costs and days of school missed.

Asthma exacerbation treatment guidelines emphasize the timely use of evidence-based pharmacotherapy (11,12). Studies have investigated the efficacy of medications for asthma exacerbations (13–20). In particular, the latest guidelines for asthma management generally highlight the use of inhaled glucocorticoids as the first option to treat moderate and severe pediatric asthma patients. Such guidelines come from better understanding of the progress of disease and the mechanism of medications. Specifically, since the importance of airway inflammation in the

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development of acute asthma has been revealed, the use of glucocorticoids, which have a strong anti-inflammatory effect, has been recommended.

Recent studies have been carried out to clarify the importance of using glucocorticoids with respect to the timing of administration (21–26). In particular, some studies have shown that glucocorticoids administered to patients with acute asthma within approximately one hour can significantly reduce the rate of emergency room revisits and admission rates (21–23). However, we found no studies evaluating the impact of the temporal sequence of medication administration.

To address this gap, we study the frequency distribution of the most common sequences of asthma medications administered to children for asthma exacerbations in one ED and then examine whether there is an association between ED outcomes and glucocorticoids timing – measured both as sequence-placement and as the traditional measure, time to first glucocorticoids (TTFS), which is defined as the elapsed time from ED arrival to the time of glucocorticoids administration for each encounter. In addition, we analyze the effect of the sequence placement of glucocorticoids administration in patients' treatment sequences on two common ED treatment outcomes – length of stay and admission rate.

Materials and methods

Study design

We performed a retrospective cohort study using electronic health record data from an urban, academic, tertiary children's hospital ED with 48 patient rooms and an annual census during the study period of 75,000 visits. We first clustered sequences of medicine prescription to identify which prescription patterns were frequently used in the ED and to analyze the temporal aspect of treatment sequences. Then, using the identified prescription patterns, we further analyzed the association between the sequence placement of administering glucocorticoids and ED treatment outcomes. This study was approved by the Colorado Multiple Institutional Review Board. Asthma care in the ED is guided by a clinical care guideline (27) based on the National Institutes of Health EPR 3 Guidelines on Asthma (28).

Data collection and processing

Data were extracted using Crystal Reports (Business Objects, San Jose, CA) to query data in Epic® (Epic Systems Corporation, Verona, WI) electronic health

records. We confirmed data quality and validity using methods described elsewhere (29,30). For the study period January 1, 2009, to December 31, 2013, we included all ED visits for patients aged 2–21 years with a primary diagnosis of acute asthma (International Classification of Disease, 9th revision (ICD-9) codes 493.xx) who received either a rescue medication or a systemic glucocorticoid (both categories defined later in this section). Each encounter contains the triage level (Emergency Severity Index (ESI) – a five-level ED triage score with 1 the most severe illness (31), ED crowding level when the encounter arrived at ED, the encounter's medication history (pharmacy class, drug name, description, and time of drug administration), the treatment outcomes (length of stay in the ED, and ED disposition), and time-stamps for all events. Encounters under 2 years or over 21 years were excluded based on common criteria used in prior studies; we also performed a sensitivity analysis on the subgroup of patients under 18 years (32–36). We also excluded encounters with ESI 1 and 5 data because of a low visit counts (13 for ESI 1, 105 for ESI 5), leaving 4,844 encounters in the final dataset for analysis. We also performed a sensitivity analysis including those in ESI group 5.

We defined two encounter outcome variables. One was the ED length of stay, which is defined as the duration in minutes from the patient's arrival to their ED departure. The other was the ED disposition, which was binary: discharge and admission.

We used the pharmacy classification variable provided to categorize medications as asthma rescue medications and systemic glucocorticoids. Fifteen different asthma-related medicines were found in our dataset. Of these, we categorized the following as rescue medications: Albuterol, Ipratropium Bromide, Ipratropium HFA, Levalbuterol HCl, Levalbuterol Tartrate, and Ipratropium-Albuterol. We categorized the following as systemic glucocorticoids: Dexamethasone, Dexamethasone Sodium Phosphate, Methyl-prednisolone, Methyl-prednisolone Acetate, Methyl-prednisolone Sodium Succinate, Prednisolone Acetate, Prednisolone Sodium Phosphate, Prednisone, and Prednisolone. We also examined the use of magnesium and terbutaline, but excluded visits with these medications due to low numbers: Only 112 visits involved magnesium and 27 received terbutaline during their ED visit. Pharmacy class, drug name, and description were coded as a string type variable; the time of medication administration, which is defined as the time elapsed since the arrival of the patient to the medication administration, was coded as a numeric variable.

Each encounter's triage level was coded by an ordinal ESI value. ED crowding level was computed by using an average hourly ED volume. Specifically, to explicitly define whether ED crowding was present at the time of each patient's arrival, we computed an average hourly ED volume for each year and then the 75th percentile was applied to define a threshold for ED crowding, based on prior studies (37–39). We assigned a binary crowding value to each encounter based on the number of patients present in the ED at the hour of ED arrival for each encounter.

Data analysis

To effectively describe patterns of asthma medication sequences, we used two categories of asthma-related treatments – rescue medications and glucocorticoids – as a basic unit for the analysis. Then, we used an exact string matching algorithm which is one of the appropriate techniques used to obtain a set of representative medication sequences from our dataset (40).

This algorithm begins with two sets: one is an empty set called the clustered set, and the other is the original set. The key idea of the algorithm is to iteratively traverse the original set to find exactly the same element (i.e., a temporal sequence of medications). The result is the set of temporal sequence and their frequency.

To determine how treatment sequence patterns vary by patients' ESI level for particular encounters and ED crowding, we conducted the same analysis, first stratified by the three included ESI levels and second stratified by crowded and non-crowded ED status.

Next, we investigated how the sequence placement of administering systemic glucocorticoids affects the outcomes, length of stay and the admission rate, and how the glucocorticoids sequence placement variable differs from TTFS measure in predicting outcomes. To compare these measures among a more homogeneous group of treatment sequences, we selected those visits with a treatment sequence of four to six asthma-related medicines. Within this subgroup, we compared the effect of assessing glucocorticoids timing by two approaches – the common approach of measuring time from arrival to first glucocorticoids (TTFS) versus sequence placement of glucocorticoids administration – on treatment outcomes. We categorized TTFS as “early TTFS” if the time between ED arrival and glucocorticoids administration was less than or equal to the 1st quartile of the distribution of TTFS durations; if it was between the 1st and 2nd quartiles, we

set this encounter as “moderate TTFS”, and all others were categorized as “late TTFS”. Similarly, we categorized sequence placement of glucocorticoids administration into three categories. If patients were administered glucocorticoids as the first or second step of their treatment sequences, we set them as “early step glucocorticoids”, if patients were administered glucocorticoids in the third or fourth step in their treatment sequences, we counted them as “moderate step glucocorticoid” and those receiving glucocorticoids fifth or later were “late step glucocorticoid”. We grouped those with glucocorticoids administered first or second into one category because in the study ED, it is often faster to administer the initial rescue medication than the initial glucocorticoid, and we did not want to create a distinction based on this pragmatic medication delivery factor.

In this analysis, we applied the one-way ANOVA test and the Kruskal–Wallis test where appropriate. We used a value of $\alpha = 0.05$ for statistical significance. In addition, we imported all data into Java (a computer programming language) for the first phase of the analysis and into R for the second phase of the analysis (41).

Results

Descriptive statistics

Of the 4,844 encounters (2,829 patients), study subjects had male predominance (62%), an average age of 7.30 years and 57% had a moderate triage level (ESI 3). The average length of stay was 5.78 h, and 30% had an ED disposition of admission (Table 1).

In Table 2, we presented information on medicines administered to study populations. The mean number of medicines administered for each encounter was 5.57, 80% of encounters included a glucocorticoid administration and for 20% of these, a glucocorticoid

Table 1. Characteristics of study population by visit ($n = 4,844$).

Variable	Frequency (proportion)
Gender	
Female	1 837 (38%)
Male	3 007 (62%)
Age (median; IQR) (years)	6.00; 6.00 (10.00 – 4.00)
Triage level (ESI)	
ESI 2	7%
ESI 3	2 781 (57%)
ESI 4	1 264 (26%)
Length of stay (average; standard deviation) (hours)	5.78 (3.61)
ED disposition (# of encounters)	
Discharge	3 416 (70%)
Admit	1 428 (30%)

Note. ESI, emergency severity index.

Table 2. Asthma-related medication delivery measures, by triage level and crowding level ($n = 4,844$).

Variable	All (4,844)	ESI level			ED crowding	
		ESI 2 (799)	ESI 3 (2,781)	ESI 4 (1,264)	Not crowded (3,158)	Crowded (1,686)
All visits (row percentage)	4,844	799 (16%)	2,781 (57%)	1,264 (26%)	3,158 (65%)	1,686 (35%)
Medication doses administered (mean)	5.57	7.61	5.94	3.47	5.59	5.37
Time to first medication (minutes)	84.99	58.27	83.16	105.93	79.17	95.91
Average (SD) of Length of stay (hours)	5.78 (3.61)	6.70 (4.01)	6.01 (3.50)	4.71 (3.35)	5.75 (3.50)	5.84 (3.82)
ED disposition (# of encounters)						
Discharge	3,416 (70%)	470 (59%)	833 (31%)	125 (10%)	2,254 (71%)	1,162 (69%)
Admit	1,428 (30%)	329 (41%)	1,885 (69%)	1,139 (90%)	904 (29%)	524 (31%)
Proportion of visits during which glucocorticoids were administered (%)	80.35	88.99	83.50	67.96	80.68	79.70
Variable	All	ESI 2	ESI 3	ESI 4	Not crowded	Crowded
All visits during which glucocorticoids were given (row percentage)	3,892	711 (15%)	2,322 (48%)	859 (18%)	2,548 (53%)	1,344 (28%)
Glucocorticoid doses administered (mean)	1.33	1.46	1.34	1.22	1.32	1.37
Proportion of visits during which glucocorticoids were first asthma medication administered (%)	23.27	2.99	13.52	6.75	15.46	7.80
TTFS (minutes)	118.98	96.54	121.42	130.94	111.63	132.90
Average steps ^a of administering glucocorticoids	2.95	3.39	3.02	2.38	2.98	2.88

^aStep represents the prescribing order in sequence of asthma-related medications.

was the initial medication given. TTFS for each encounter averaged 85 min (median: 66 min) and TTFS was 118.98 min (median: 96.5 min) from arrival. The mean and median (IQR) order of glucocorticoid dosing in the asthma medication sequence were 2.95 and 3 [(1/4, 3/4 quartile) = (1, 4)].

The results of the identified characteristics from stratified sub-sets showed that the mean number of medication doses used increased with increasing encounter ESI severity (7.61 for ESI 2 versus 3.47 for ESI 4). The proportion of encounters who received glucocorticoid increased with rising encounter ESI severity (89% for ESI 2 versus 68% for ESI 4), although the proportion of encounters where patients given glucocorticoid as the first medication decreased with rising ESI severity (18.2% for ESI 2 versus 25.9% for ESI 4). Similarly, in ESI 4 group of encounters were more likely to receive glucocorticoid in earlier stage of their treatment sequence compared to the group of ESI 2 (3.39 steps for ESI 2 versus 2.38 steps for ESI 4).

In bivariate analyses by ED crowding level, we found a significant difference in the time to first medication (79.17 min for noncrowded versus 95.91 for crowded), and TTFS (111.63 min for noncrowded versus 132.90 for crowded). For all other factors, we confirmed that there was no statistically significant difference between the two groups with respect to ED crowding level.

Results of the analysis

Clustering treatment sequences

The ten most frequently used medicine prescription sequences accounted for 43% of all encounters (Table

Table 3. The proportion of asthma medication treatment sequences represented by the 10, 20 and 30 most common sequences by triage level and crowding level ($n = 4,844$).

	All (%)	ESI 2 (%)	ESI 3 (%)	ESI 4 (%)
Top 10	43.00	32.90	38.70	64.20
Top 20	60.60	46.60	57.20	79.40
Top 30	69.70	56.20	67.70	85.10

3), and the top 20 and 30 sequences accounted for 60.6% and 69.7% of all encounters respectively. Among them, the most commonly used prescription pattern was the use of a single dose of rescue medication, albuterol (11.9%).

The stratified analyses showed that ESI severity was inversely correlated with the proportion of treatment sequences accounted for by the top ten treatment sequences. For encounters with ESI 2, the top 10 treatment sequences accounted for 32.9% of visits, while 64.2% of ESI 4 visits were represented by the top 10 treatment sequences. Table 4 shows the 10 most common treatment sequences overall and by ESI level. As shown in this Table 4, although the ranking varied by the ESI level, the treatment sequences represented in each list were similar.¹

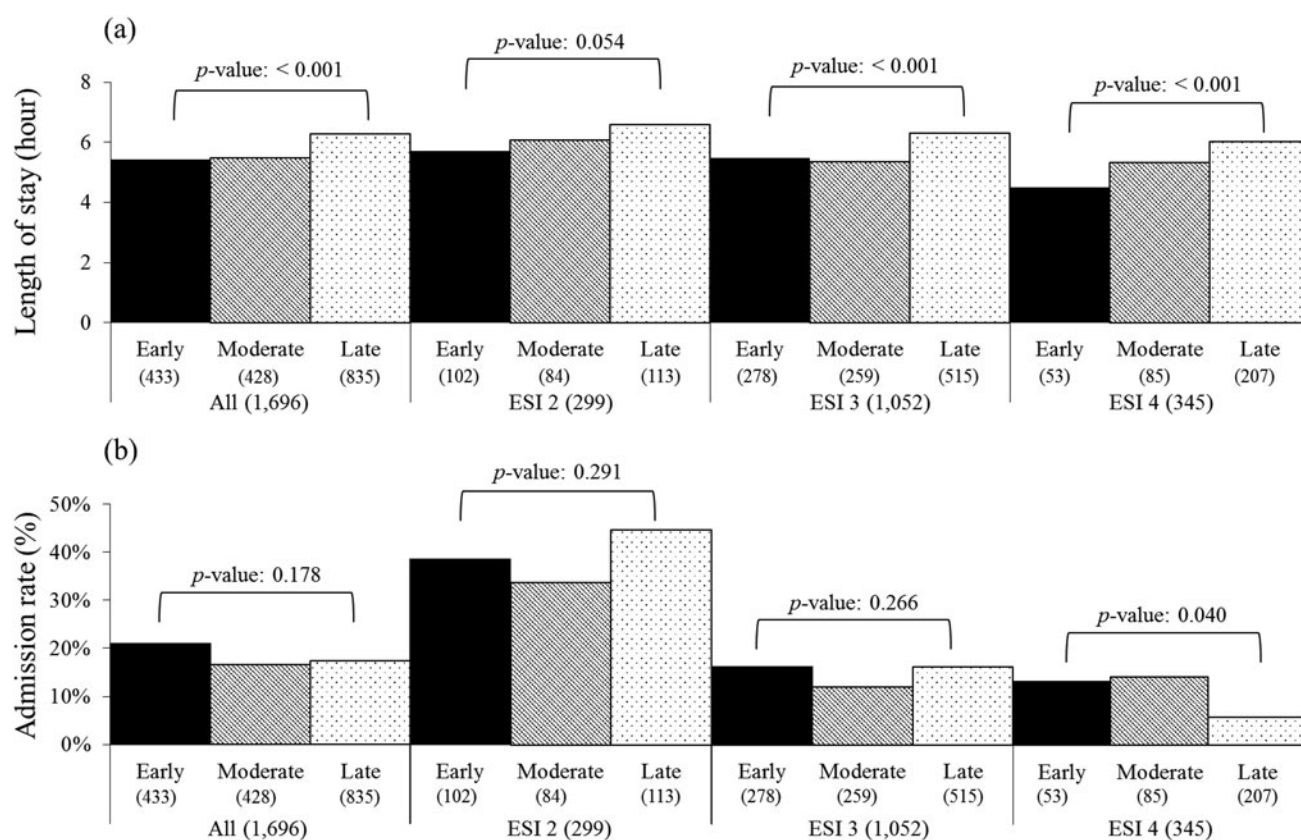
Association between TTFS, sequence placement and outcomes

Figure 1 presents the association between TTFS and two treatment outcomes. Specifically, earlier TTFS was positively correlated with a shorter length of stay. Encounters with early TTFS show an average length of stay of 5.42 h, whereas those with late TTFS averaged 6.27 h ($p < 0.001$). By ESI stratum, this association was significant for ESI 3 and 4, and demonstrated a nonsignificant trend towards

Table 4. The ten most common asthma treatment sequences by encounter severity ($n = 4,844$).

Rank	Total		ESI 2		ESI 3		ESI 4	
	Treatment sequence	Count (%)	Treatment sequence	Count (%)	Treatment sequence	Count (%)	Treatment sequence	Count (%)
1	R	576 (11.9%)	R	35 (4.4%)	R	228 (8.2%)	R	313 (24.8%)
2	S	274 (5.7%)	R-R-R-S-R	34 (4.3%)	R-R-R-S-R	143 (5.1%)	S	119 (9.4%)
3	R-S	244 (5.0%)	R-R-R-R-S	32 (4.0%)	R-S	127 (4.6%)	R-S	106 (8.4%)
4	R-R-R-S-R	221 (4.6%)	S	29 (3.6%)	S	126 (4.5%)	S-R	58 (4.6%)
5	S-R	163 (3.4%)	R-R-R-R-S-R	29 (3.6%)	S-R	94 (3.4%)	R-R	49 (3.9%)
6	R-R-R-S	142 (2.9%)	R-R-S-R-R	28 (3.5%)	R-R-R-S	93 (3.3%)	R-R-R-S-R	44 (3.5%)
7	R-R	137 (2.8%)	R-R-R-S	22 (2.8%)	R-R	75 (2.7%)	S-R-R-R	33 (2.6%)
8	R-R-R-R-S	110 (2.3%)	R-R-R-S-R-R	22 (2.8%)	S-R-R-R-R	68 (2.4%)	R-R-S	32 (2.5%)
9	R-R-R-R-S-R	110 (2.3%)	S-R-R-R-R	18 (2.3%)	R-R-R-R-S-R	63 (2.3%)	R-R-S-R	31 (2.5%)
10	S-R-R-R-R	107 (2.2%)	R-R-R	14 (1.8%)	R-R-R-S-R-R	58 (2.1%)	R-R-R-S	27 (2.1%)
Total		4,844 (100%)		799 (100%)		2,781 (100%)		1,264 (100%)

Note. R, rescue medication; S, glucocorticoids.

**Figure 1.** The association between the TTFs and treatment outcomes (Length of stay, admission rate) ($n = 1,696$).

† Early: TTFs ≤ 58 minutes (1st quartile of the distribution of TTFs); Moderate: TTFs 59 – 91 minutes (2nd quartile of the distribution of TTFs); Late: TTFs > 91 minutes.

increased length of stay with later TTFs for the group with ESI 2. Conversely, TTFs was not associated with admission rate for any ESI stratum. Specifically, the average admission rates were 21.0%, 16.6% and 17.4% for the early, moderate and late TTFs groups, respectively.

The sequence placement of glucocorticoids administration was associated with both a shorter length of stay and a lower admission rate (Figure 2). With each step later for the order of glucocorticoids in the

sequence, the admission rate consistently rose from 15.0% to 28.7% ($p < 0.001$). When stratified by ESI level, earlier step glucocorticoids were positively correlated with the shorter length of stay except for the group with ESI 2, and was associated with lower admission rates for patients in ESI 2 and 3 type encounter, with a nonsignificant trend. However, in terms of admission rate, the less admission rate was expected as patients receive glucocorticoids in the earlier stage of their medication patterns during and

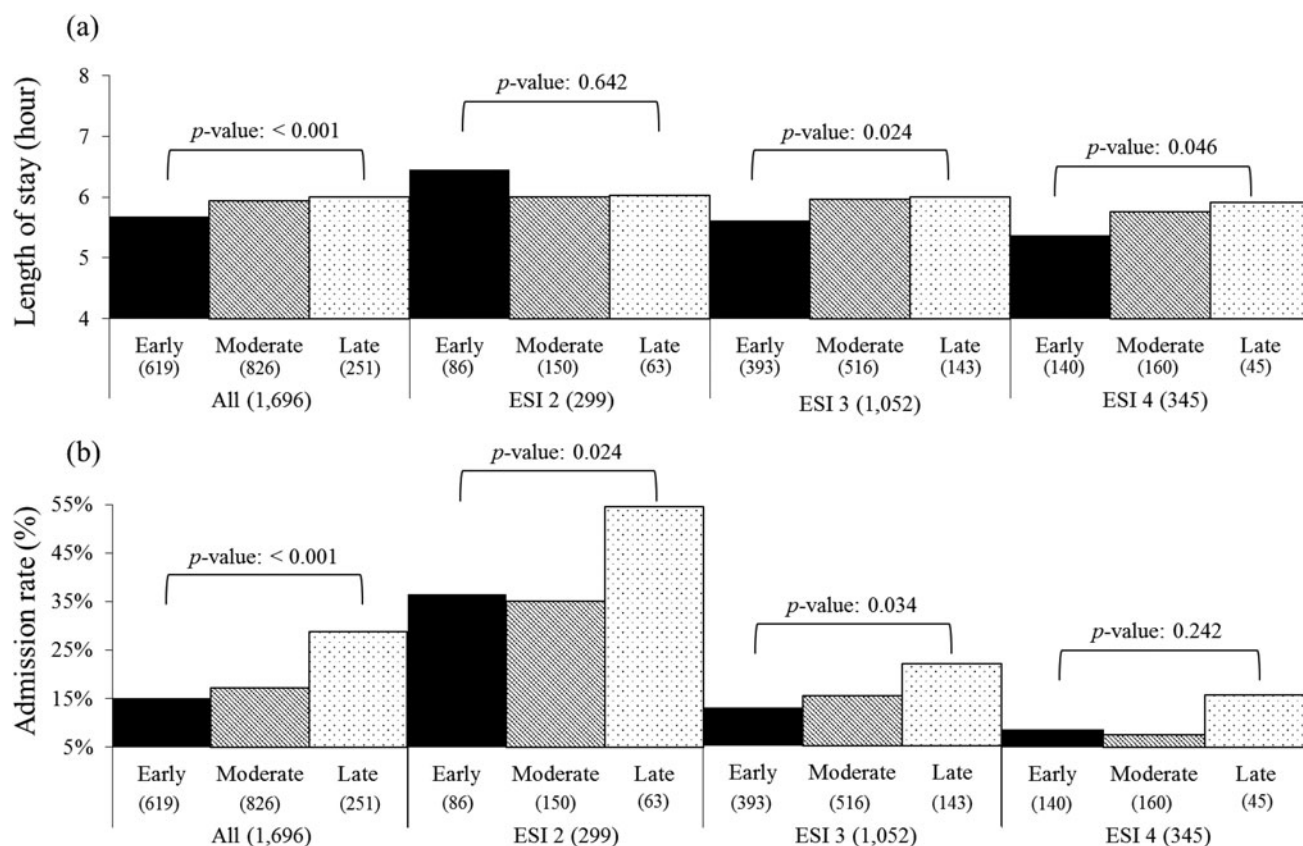


Figure 2. The association between the sequence placement of glucocorticoids and treatment outcomes ($n = 1,696$).

† Early: Administered glucocorticoid at the first or second step of treatment sequence; Moderate: Administered glucocorticoid at the third or fourth step of treatment sequence; Late: Glucocorticoid administered at or after 5th step.

Table 5. The effect of the order of administering glucocorticoids according to the TTFS ($n = 1,696$).

TTFS ^a (n)	The order of glucocorticoids administration (n)	Average of length of stay (hours)	p-value	Admission rate (%)	p-value
Early (≤ 58 minutes) (433)	Early (246)	5.19	0.116	16.7	0.004
	Moderate (161)	5.75		24.2	
	Late (26)	5.43		42.3	
Moderate (≤ 91 minutes) (428)	Early (165)	5.36	0.039	13.9	0.474
	Moderate (197)	5.47		17.8	
	Late (66)	5.82		19.7	
Late (> 91 minutes) (853)	Early (208)	6.50	0.326	13.9	<0.001
	Moderate (468)	6.19		14.5	
	Late (159)	6.17		30.2	

^aTime to first glucocorticoid administration.

encounter. This was significant for ESI 2 and 3, and demonstrated a similar but nonsignificant trend for ESI 4.²

When stratified by TTFS, the sequence placement of glucocorticoids administration was associated with a lower admission rate, but not with a shorter length of stay (Table 5). Within the early and late TTFS subgroups, increasing from early to moderate to late step glucocorticoids was associated with increasing admission rate. This trend was also noted in the moderate TTFS subgroup but was nonsignificant. Results of our

sensitivity analysis including encounters in ESI group 5 are also in Supplemental Materials.

Discussion

For pediatric asthma patients treated in EDs, asthma management guidelines recommend the timing and sequence of medications according to patients' severity and response to therapy (11,12). To the best of authors' knowledge, ours is the first study to describe the sequence of asthma medicine administration in

clinical practice and the impact of this sequence on treatment outcomes.

Our main finding was that the order of glucocorticoids in the asthma medication sequence was associated with patients' ED encounter-linked asthma outcomes—specifically, a shorter length of stay and lower admission rate. Based on prior research showing glucocorticoids delivery early in the ED course improves asthma exacerbation treatment outcomes (21–26), multiple quality improvement projects have used TTFS as a performance metric for the quality of ED asthma care (42,43). In our analyses, a shorter TTFS contributed to better treatment outcome (length of stay) but was not associated with the admission rate. Our analyses of the association between the sequence placement of glucocorticoid administration and treatment outcomes provided a new insight on predicting patients' treatment outcomes from the ED encounter. Our statistical results revealed that that using glucocorticoids earlier in the treatment sequence was associated with lower admission rate, regardless of the ESI level. The results and implication were still valid, even for the case of a shorter TTFS (within 58 min). The earlier introduction of glucocorticoids in the ED visit might enhance β -agonists' effects through reducing inflammation and bronchial hyper-responsiveness, which might ultimately help to improve patients' treatment outcomes (encounter-related length of stay, admission rate) (44).

Thus, both the sequence order and the timing of glucocorticoid administration are likely contributory to patient outcomes. The pair of measures may prove more effective than either one in isolation in guiding interventions aimed at improving patient outcomes. That is, our new measure can act as a complementary measure with the traditional TTFS measure.

A second key finding was that the diversity of asthma medication sequences increases with increasing severity of ESI level. For encounters with ESI 2, the top 10 treatment regimens only account for 32.9% of the patients with ESI 2 encounters, while they account for 64.2% of ESI 4 group. This may reflect the guidelines' recommendations of a broader array of medications for patients with severe asthma exacerbations than for those with milder flares. Our analysis excluded medications like magnesium and terbutaline – medications indicated for the more severe exacerbations, and thus our findings may underestimate the diversity of sequences for patients with ESI 2 severity. It is beyond the scope of this analysis to determine whether the diversity of treatment sequences reflects deviations from standardized treatment protocols

(45–47) or care driven by multiple determinants in addition to guideline recommendations.

Third, we found that ED crowding impacts the timeliness of medication delivery but not the treatment sequence. This is demonstrated by the fact that most asthma medication delivery indicators (Table 2) did not differ by ED crowding. This differs from prior studies that indicated ED crowding was a barrier to timely ED asthma care (48,49).

Our approach and findings suggest that adding asthma medication sequence to clinical process improvement efforts may enhance ED care for asthma exacerbations. For example, an alert that reminds providers to order glucocorticoids after the second rescue medication is administered may improve the timeliness of glucocorticoid dosing within the asthma medication sequence, and thereby improve length of stay and admission rates (50). More generally, by considering first clinical interventions and real-time condition of the patient, clinical decision support systems (CDSS) can guide clinicians for the next steps. Temporal (e.g. sequential) perspectives provide critical insights for the development of CDSS by providing the needed information in a timely manner and at the right point in the clinical workflow (51,52).

Limitations

Our study has several limitations. First, because our analyses were conducted in a retrospective manner, errors in data measurement and collection are possible. We attempted to mitigate these errors by using an established procedure to verify the quality and validity of our data. Second, the only non-clinical determinant of medication sequence we considered was crowding, and multiple unmeasured factors such as patient vomiting oral medications or difficulty getting intravenous access may impact when glucocorticoids were given in a medication sequence – just as they influence TTFS. Also, some of these factors are not amenable to change – such as the propensity of a preschooler to fight glucocorticoid administration – or even inappropriate to change – such as the need to administer multiple rescue medications initially for a patient who comes to the visit with severe respiratory distress. Third, provider practice pattern variation may have confounded our findings, in that providers who prescribe medications in a specific sequence may also differ in their propensity to admit patients to the hospital or discharge them early. As our data lacked provider identifiers, identifying provider-level confounding was beyond the scope of this analysis. A fourth limitation is the clustering level we used. Due

to the granularity of data we had, we clustered treatment sequences by a medicine type (rescue medication or glucocorticoids). Since there are a variety of medication administration protocols (dose level, routes, etc.), considering those factors in the analysis may increase the quality of analysis and provide more insightful results which can be used in practice. A fifth limitation is that we conducted our analysis in one ED setting. Since the treatment sequences can vary by context, the generalization of our findings is limited.

Despite these limitations, our study demonstrates the value of information in evaluating asthma medication sequences in ED care for acute asthma exacerbations—both in determining the association between medication sequence and ED outcomes and in illustrating the non-uniformity of care sequences present with escalating severity. Future studies involving asthma-specific severity indicators and diverse acute care clinical settings can broaden the generalizability of our findings in guiding data-driven clinical process improvement metrics and interventions that include medication sequence.

Conclusions

Our analysis of medication sequence patterns for pediatric asthma patients treated during their visit (encounter) to a single emergency department found that the sequence placement of glucocorticoid administration plays an important role in predicting patients' treatment outcomes. The addition of medication sequence to more conventional metrics such as TTFS, can help improve our understanding of how to improve patients' treatment outcomes during asthma episodes and may, ultimately, help us strengthen our treatment guidelines for pediatric asthma.

Notes

1. We conducted another stratified analyses according to ED crowding level, and found that the top 10 list of treatment sequences did not significantly differ, and therefore we do not report the detailed results.
2. Because we used a large-size dataset collected over many years, some could be entered the ED multiple times (multiple visits by the same patients), and this may have distorted our key findings. To examine whether this affects our key findings, we have conducted additional experiments. The experimental results show that our key findings are still valid, even when such duplications are eliminated. The detailed experimental results are provided in the [Supplemental Materials](#).

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Supplemental Material

1. Sensitivity Analysis on Different Upper Age Limit

To verify the robustness of our key findings to age inclusion criteria, we conducted a sensitivity analysis to determine whether limiting the analysis to those patients younger than 18 years old produced different findings. We found no differences from those in the primary analysis (Figures 1 and 2). Specifically, earlier sequence placement of administering corticosteroids to pediatric asthma patients was positively correlated with better treatment outcomes – shorter length of stay and lower admission rate.

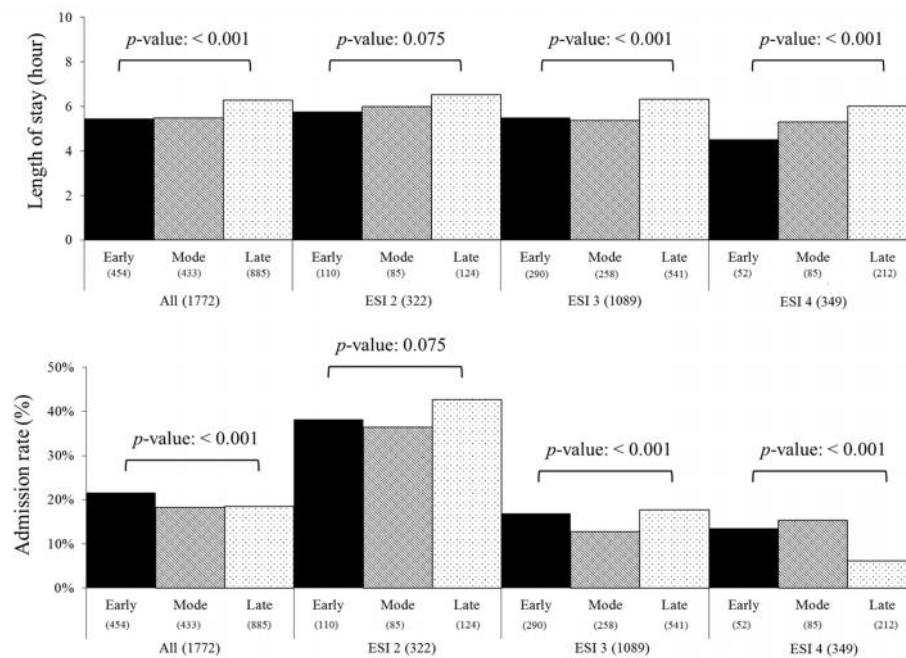


Figure 1. The association between the TTFS and treatment outcomes

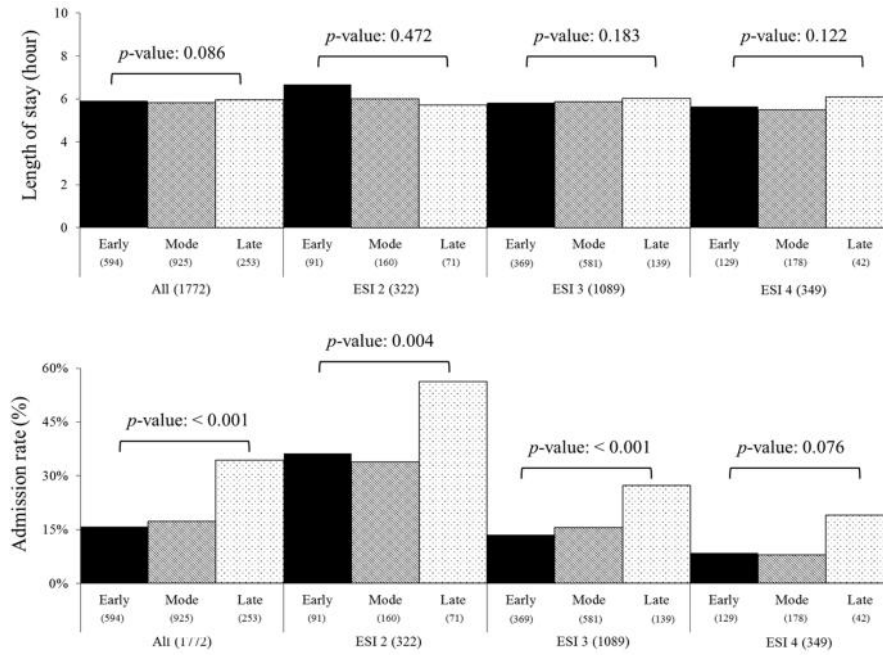


Figure 2. The association between the sequence placement of corticosteroids and treatment outcomes

2. Sensitivity Analysis in First Visits Excluding All But One Visit for Patients with Multiple Visits

Because we used a large timeframe (data collected 2009 – 2013), a patient can enter the ED multiple times. To examine the effect of multiple visits by the same patient, we prepared a new dataset. For patients with multiple visits, we randomly selected one visit per patient. After eliminating subsequent encounters, we conducted examined whether multiple encounters (multiple entries per patient) affected our key research findings on the remaining dataset (930 encounter records).

Similar to the primary analysis, there still exists a positive correlation between the earlier placement of corticosteroids and better treatment outcomes (Figures 3 and 4).

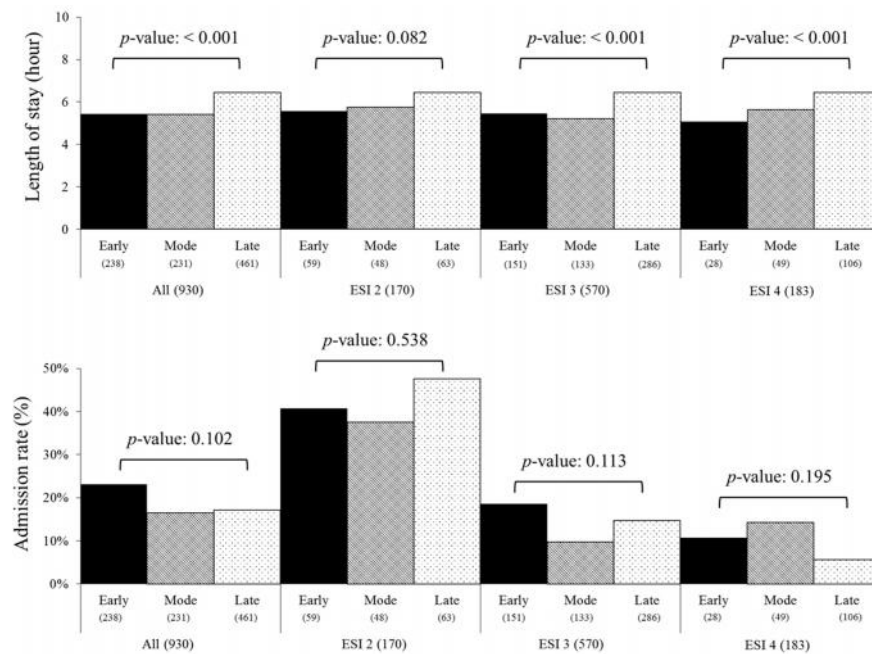


Figure 3. The association between the TTFS and treatment outcomes

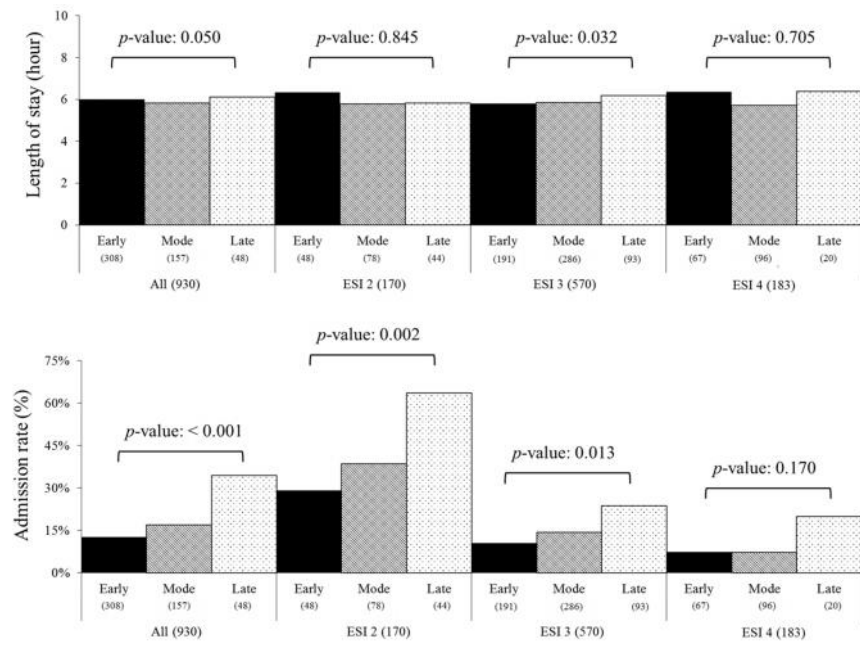


Figure 4. The association between the sequence placement of corticosteroids and treatment outcomes

3. Analysis on the group of ESI 1 and 5

We excluded ESI 1 and ESI 5 (the most and the least urgent, respectively) data because of the low counts compared with populations in other ESI levels. Specifically, the number of encounters belonging to ESI 1 and 5 were 13 and 105, respectively. Because encounters in ESI 1 is too small numbers to conduct valid statistical tests, we only included encounters in ESI 5 for the statistical tests to determine if there exists an association between TTFS (or sequence placement) and treatment outcomes. The results are shown as follows:

Table 1 The association between TTFS and treatment outcomes

	TTFS	N	Length of Stay (Hour)	p-value	Admission rate (%)	p-value
ESI 5	Early	5	3.260	< 0.001	0.0%	0.302
	Mode	13	2.430		0.0%	
	Late	32	5.161		12.5%	

Table 2 The association between the sequence placement of corticosteroids and treatment outcomes

	The sequence of corticosteroids	N	Length of Stay (Hour)	p-value	Admission rate (%)	p-value
ESI 5	Early	38	3.565	< 0.001	0.0%	< 0.001
	Mode	10	6.278		40.0%	
	Late	2	7.392		0.0%	

As presented in the Table2, there exists a statistically significant association between the time to first corticosteroid is administered and a shorter length of stay, similar to the results obtained with other groups (ESI 2 – 4). Also, we found a positive correlation between the earlier administration of corticosteroids with patients' treatment outcomes (length of stay, admission rate; p-value < 0.001).