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ORIGINAL RESEARCH

Medications Associated With Clinical Deterioration in Hospitalized Children

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BACKGROUND: Medical emergency teams have been shown to reduce mortality in children's hospitals, but there are many potential barriers to their activation. Surveillance tools using electronic health record data help identify children at risk of deterioration. Existing early warning scores primarily include vital signs, but may benefit from the incorporation of medications.

OBJECTIVE: We aimed to identify the therapeutic classes of medications temporally associated with clinical deterioration that could be incorporated with vital signs into surveillance tools.

DESIGN: Case-crossover study.

SETTING: The Children's Hospital of Philadelphia.

PATIENTS: Children with clinical deterioration, defined as cardiopulmonary arrest, acute respiratory compromise, or urgent intensive care unit transfer while hospitalized on pediatric wards (n = 141).

EXPOSURES: Intravenous administrations of medications from therapeutic classes administered in ≥5% of control periods.

RESULTS: Nine therapeutic classes were significantly associated with clinical deterioration: glycopeptide antibiotics, anaerobic antibiotics, third-generation and fourth-generation cephalosporins, aminoglycoside antibiotics, systemic corticosteroids, benzodiazepines, loop diuretics, narcotic analgesics (full opioid agonists), and antidotes to hypersensitivity reactions.

CONCLUSIONS: We identified a set of therapeutic classes associated with increased risk of clinical deterioration. Future work should focus on evaluating whether including these therapeutic classes in multivariable models improves their accuracy in detecting early, evolving deterioration. *Journal of Hospital Medicine* 2013;8:254–260. © 2013 Society of Hospital Medicine

In recent years, many hospitals have implemented rapid response systems (RRSs) in efforts to reduce mortality outside the intensive care unit (ICU). Rapid response systems include 2 clinical components (efferent and afferent limbs) and 2 organizational components (process improvement and administrative limbs).[1,2] The efferent limb includes medical emergency teams (METs) that can be summoned to hospital wards to rescue deteriorating patients. The afferent limb identifies patients at risk of deterioration using tools such as early warning scores and triggers a MET response when appropriate.[2] The process-improvement limb evaluates and optimizes the RRS. The administrative limb implements the RRS and supports its ongoing operation. The effectiveness of most RRSs depends upon the ward team making the decision to escalate care by activating the MET. Barriers to activating the MET may include reduced situational awareness,[3,4] hierarchical barriers to calling for help,[3–8] fear of criticism,[3,8,9] and other hospital safety cultural barriers.[3,4,8]

Proactive critical-care outreach[10–13] or rover[14] teams seek to reduce barriers to activation and improve outcomes by systematically identifying and evaluating at-risk patients without relying on requests for assistance from the ward team. Structured similarly to early warning scores, surveillance tools intended for rover teams might improve their ability to rapidly identify at-risk patients throughout a hospital. They could combine vital signs with other variables, such as diagnostic and therapeutic interventions that reflect the ward team's early, evolving concern. In particular, the incorporation of medications associated with deterioration may enhance the performance of surveillance tools.

Medications may be associated with deterioration in one of several ways. They could play a causal role in deterioration (ie, opioids causing respiratory insufficiency), represent clinical worsening and anticipation

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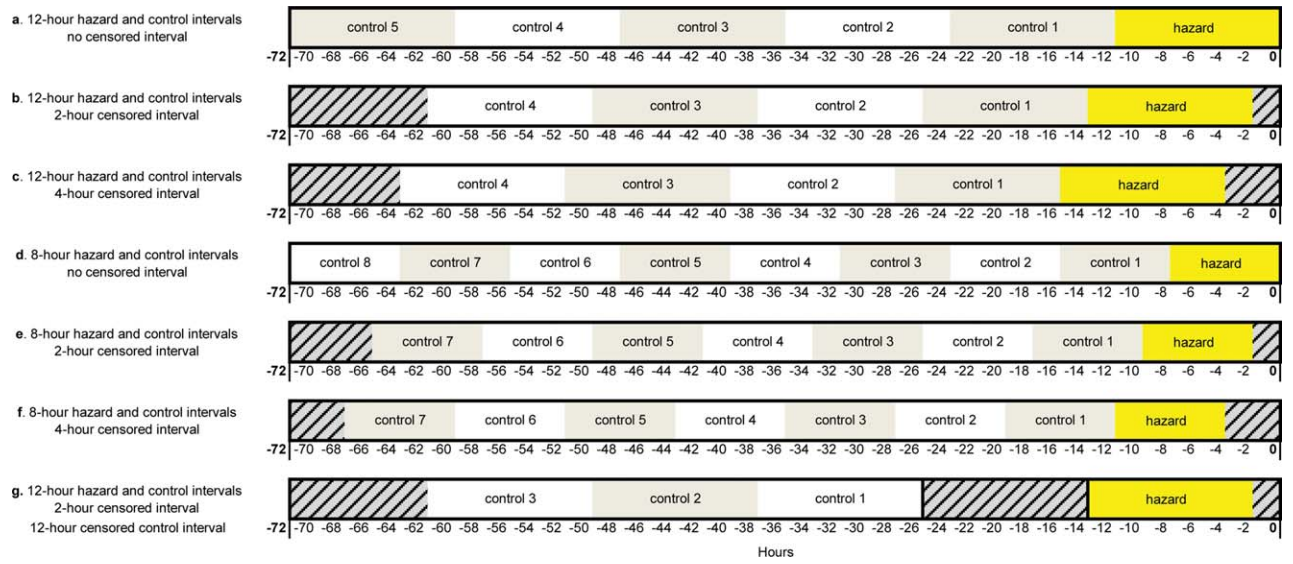

FIG. 1. Schematic of the iterations of the sensitivity analysis. (A–F) The length of the hazard and control intervals was either 8 or 12 hours, whereas the length of the censored interval was either 0, 2, or 4 hours. (B) The primary analysis used 12-hour hazard and control intervals with a 2-hour censored interval. (G) The design is a variant of the primary analysis in which the control interval closest to the hazard interval is censored.

of possible deterioration (ie, broad-spectrum antibiotics for a positive blood culture), or represent rescue therapies for early deterioration (ie, antihistamines for allergic reactions). In each case, the associated therapeutic classes could be considered sentinel markers of clinical deterioration.

Combined with vital signs and other risk factors, therapeutic classes could serve as useful components of surveillance tools to detect signs of early, evolving deterioration and flag at-risk patients for evaluation. As a first step, we sought to identify therapeutic classes associated with clinical deterioration. This effort to improve existing afferent tools falls within the process-improvement limb of RRSs.

PATIENTS AND METHODS

Study Design

We performed a case-crossover study of children who experienced clinical deterioration. An alternative to the matched case-control design, the case-crossover design involves longitudinal within-subject comparisons exclusively of case subjects such that an individual serves as his or her own control. It is most effective when studying intermittent exposures that result in transient changes in the risk of an acute event,[15–17] making it appropriate for our study.

Using the case-crossover design, we compared a discrete time period in close proximity to the deterioration event, called the "hazard interval," with earlier time periods in the hospitalization, called the "control intervals."[15–17] In our primary analysis (Figure 1B), we defined the durations of these intervals as follows: We first censored the 2 hours immediately preceding the clinical deterioration event (hours 0 to −2). We made this decision a priori to exclude medications used after deterioration was recognized and resuscitation had already begun. The 12-hour period immediately preceding the censored interval was the hazard interval (hours −2 to −14). Each 12-hour period immediately preceding the hazard interval was a control interval (hours −14 to −26, −26 to −38, −38 to −50, and −50 to −62). Depending on the child's length of stay prior to the deterioration event, each hazard interval had 1–4 control intervals for comparison. In sensitivity analysis, we altered the durations of these intervals (see below).

Study Setting and Participants

We performed this study among children age <18 years who experienced clinical deterioration between January 1, 2005, and December 31, 2008, after being hospitalized on a general medical or surgical unit at The Children's Hospital of Philadelphia for ≥24 hours. Clinical deterioration was a composite outcome defined as cardiopulmonary arrest (CPA), acute respiratory compromise (ARC), or urgent ICU transfer. Cardiopulmonary arrest events required either pulselessness or a pulse with inadequate perfusion treated with chest compressions and/or defibrillation. Acute respiratory compromise events required respiratory insufficiency treated with bag-valve-mask or invasive airway interventions. Urgent ICU transfers included ≥1 of the following outcomes in the 12 hours after transfer: death, CPA, intubation, initiation of noninvasive ventilation, or administration of a vasoactive medication infusion used for the treatment of shock. Time zero was the time of the CPA/ARC, or the time at which the child arrived in the ICU for urgent transfers. These subjects also served as the cases for a previously published case-control study evaluating

different risk factors for deterioration.[18] The institutional review board of The Children's Hospital of Philadelphia approved the study.

At the time of the study, the hospital did not have a formal RRS. An immediate-response code-blue team was available throughout the study period for emergencies occurring outside the ICU. Physicians could also page the pediatric ICU fellow to discuss patients who did not require immediate assistance from the code-blue team but were clinically deteriorating. There were no established triggering criteria.

Medication Exposures

Intravenous (IV) medications administered in the 72 hours prior to clinical deterioration were considered the exposures of interest. Each medication was included in ≥1 therapeutic classes assigned in the hospital's formulary (Lexicomp, Hudson, OH).[19] In order to determine which therapeutic classes to evaluate, we performed a power calculation using the sampsi_mcc package for Stata 12 (StataCorp, College Station, TX). We estimated that we would have ≥3 matched control intervals per hazard interval. We found that, in order to detect a minimum odds ratio of 3.0 with 80% power, a therapeutic class had to be administered in ≥5% of control periods. All therapeutic classes meeting that requirement were included in the analysis and are listed in Table 1. (See lists of the individual medications comprising each class in the Supporting Information, Tables 1–24, in the online version of this article.)

TABLE 1. Therapeutic Classes With Drugs Administered in ≥5% of Control Intervals, Meeting Criteria for Evaluation in the Primary Analysis Based on the Power Calculation

Therapeutic Class	No. of Control Intervals	%
Sedatives	107	25
Antiemetics	92	22
Third- and fourth-generation cephalosporins	83	20
Antihistamines	74	17
Antidotes to hypersensitivity reactions (diphenhydramine)	65	15
Gastric acid secretion inhibitors	62	15
Loop diuretics	62	15
Anti-inflammatory agents	61	14
Penicillin antibiotics	61	14
Benzodiazepines	59	14
Hypnotics	58	14
Narcotic analgesics (full opioid agonists)	54	13
Antianxiety agents	53	13
Systemic corticosteroids	53	13
Glycopeptide antibiotics (vancomycin)	46	11
Anaerobic antibiotics	45	11
Histamine H_2 antagonists	41	10
Antifungal agents	37	9
Phenothiazine derivatives	37	9
Adrenal corticosteroids	35	8
Antiviral agents	30	7
Aminoglycoside antibiotics	26	6
Narcotic analgesics (partial opioid agonists)	26	6
PPIs	26	6

NOTE: **Abbreviations:** PPIs, proton pump inhibitors. Individual medications comprising each class are in the Supporting Information, Tables 1–24, in the online version of this article.

Data Collection

Data were abstracted from the electronic medication administration record (Sunrise Clinical Manager; Allscripts, Chicago, IL) into a database. For each subject, we recorded the name and time of administration of each IV medication given in the 72 hours preceding deterioration, as well as demographic, event, and hospitalization characteristics.

Statistical Analysis

We used univariable conditional logistic regression to evaluate the association between each therapeutic class and the composite outcome of clinical deterioration in the primary analysis. Because cases serve as their own controls in the case-crossover design, this method inherently adjusts for all subject-specific time-invariant confounding variables, such as patient demographics, disease, and hospital-ward characteristics.[15]

Sensitivity Analysis

Our primary analysis used a 2-hour censored interval and 12-hour hazard and control intervals. Excluding the censored interval from analysis was a conservative approach that we chose because our goal was to identify therapeutic classes associated with deterioration during a phase in which adverse outcomes may be prevented with early intervention. In order to test whether our findings were stable across different lengths of censored, hazard, and control intervals, we performed a sensitivity analysis, also using conditional logistic regression, on all therapeutic classes that were significant ($P < 0.05$) in primary analysis. In 6 iterations of the sensitivity analysis, we varied the length of the hazard and control intervals between 8 and 12 hours, and the length of the censored interval between 0 and 4 hours (Figure 1A–F). In a seventh iteration, we used a variant of the primary analysis in which we censored the first control interval (Figure 1G).

RESULTS

We identified 12 CPAs, 41 ARCs, and 699 ICU transfers during the study period. Of these 752 events, 141 (19%) were eligible as cases according to our inclusion criteria.[18] (A flowchart demonstrating the identification of eligible cases is provided in Supporting Table 25 in the online version of this article.) Of the 81% excluded, 37% were ICU transfers who did not meet urgent criteria. Another 31% were excluded because they were hospitalized for <24 hours at the time of the event, making their analysis in a case-crossover design using 12-hour periods impossible. Event characteristics, demographics, and hospitalization characteristics are shown in Table 2.

Primary Analysis

A total of 141 hazard intervals and 487 control intervals were included in the primary analysis, the

TABLE 2. Subject Characteristics (N = 141)

	n	%
Type of event		
CPA	4	3
ARC	29	20
Urgent ICU transfer	108	77
Demographics		
Age		
0–<6 months	17	12
6–<12 months	22	16
1–<4 years	34	24
4–<10 years	26	18
10–<18 years	42	30
Sex		
F	60	43
M	81	57
Race		
White	69	49
Black/African American	49	35
Asian/Pacific Islander	0	0
Other	23	16
Ethnicity		
Non-Hispanic	127	90
Hispanic	14	10
Hospitalization		
Surgical service	4	3
Survived to hospital discharge	107	76

NOTE: **Abbreviations:** ARC, acute respiratory compromise; CPA, cardiopulmonary arrest; F, female; ICU, intensive care unit; M, male.

TABLE 3. Results of Primary Analysis Using 12-Hour Blocks and 2-Hour Censored Period

	OR	LCI	UCI	*P* Value
Antimicrobial therapeutic classes				
Glycopeptide antibiotics (vancomycin)	5.84	2.01	16.98	0.001
Anaerobic antibiotics	5.33	1.36	20.94	0.02
Third- and fourth-generation cephalosporins	2.78	1.15	6.69	0.02
Aminoglycoside antibiotics	2.90	1.11	7.56	0.03
Penicillin antibiotics	2.40	0.9	6.4	0.08
Antiviral agents	1.52	0.20	11.46	0.68
Antifungal agents	1.06	0.44	2.58	0.89
Corticosteroids and other anti-inflammatory therapeutic classes*				
Systemic corticosteroids	3.69	1.09	12.55	0.04
Anti-inflammatory agents	3.69	1.09	12.55	0.04
Adrenal corticosteroids	3.69	1.09	12.55	0.04
Sedatives, hypnotics, and antianxiety therapeutic classes†				
Sedatives	3.48	1.78	6.78	<0.001
Benzodiazepines	2.71	1.36	5.40	0.01
Hypnotics	2.54	1.27	5.09	0.01
Antianxiety agents	2.28	1.06	4.91	0.04
Narcotic analgesic therapeutic classes				
Narcotic analgesics (full opioid agonists)	2.48	1.07	5.73	0.03
Narcotic analgesics (partial opioid agonists)	1.97	0.57	6.85	0.29
GI therapeutic classes				
Antiemetics	0.57	0.22	1.48	0.25
PPIs	2.05	0.58	7.25	0.26
Phenothiazine derivatives	0.47	0.12	1.83	0.27
Gastric acid secretion inhibitors	1.71	0.61	4.81	0.31
Histamine H_2 antagonists	0.95	0.17	5.19	0.95
Other therapeutic classes				
Loop diuretics	2.87	1.28	6.47	0.01
Antidotes to hypersensitivity reactions (diphenhydramine)	2.45	1.15	5.23	0.02
Antihistamines	2.00	0.97	4.12	0.06

NOTE: **Abbreviations:** CI, confidence interval; GI, gastrointestinal; LCI, lower confidence interval; OR, odds ratio; PPIs, proton-pump inhibitors; UCI, upper confidence interval. Substantial overlap exists among some therapeutic classes; see Supporting Information, Tables 1–24, in the online version of this article for a listing of the medications that comprised each class. *There was substantial overlap in the drugs that comprised the corticosteroids and other anti-inflammatory therapeutic classes, and the ORs and CIs were identical for the 3 groups. When the individual drugs were examined, it was apparent that hydrocortisone and methylprednisolone were entirely responsible for the OR. Therefore, we used the category that the study team deemed (1) most parsimonious and (2) most clinically relevant in the sensitivity analysis, systemic corticosteroids. †There was substantial overlap between the sedatives, hypnotics, and antianxiety therapeutic classes. When the individual drugs were examined, it was apparent that benzodiazepines and diphenhydramine were primarily responsible for the significant OR. Diphenhydramine had already been evaluated in the antidotes to hypersensitivity reactions class. Therefore, we used the category that the study team deemed (1) most parsimonious and (2) most clinically relevant in the sensitivity analysis, benzodiazepines.

results of which are shown in Table 3. Among the antimicrobial therapeutic classes, glycopeptide antibiotics (vancomycin), anaerobic antibiotics, third-generation and fourth-generation cephalosporins, and aminoglycoside antibiotics were significant. All of the anti-inflammatory therapeutic classes, including systemic corticosteroids, anti-inflammatory agents, and adrenal corticosteroids, were significant. All of the sedatives, hypnotics, and antianxiety therapeutic classes, including sedatives, benzodiazepines, hypnotics, and antianxiety agents, were significant. Among the narcotic analgesic therapeutic classes, only 1 class, narcotic analgesics (full opioid agonists), was significant. None of the gastrointestinal therapeutic classes were significant. Among the classes classified as "other," loop diuretics and antidotes to hypersensitivity reactions (diphenhydramine) were significant.

Sensitivity Analysis

Of the 14 classes that were significant in primary analysis, we carried 9 forward to sensitivity analysis. The 5 that were not carried forward overlapped substantially with other classes that were carried forward. The decision of which overlapping class to carry forward was based upon (1) parsimony and (2) clinical relevance. This is described briefly in the footnotes to Table 3 (see Supporting information in the online version of this article for a full description of this process). Figure 2B presents the odds ratios and their 95% confidence intervals for the sensitivity analysis of each therapeutic class that was significant in primary analysis. Loop diuretics remained significantly associated with deterioration in all 7 iterations. Glycopeptide antibiotics (vancomycin), third-generation and fourth-generation cephalosporins, systemic corticosteroids, and benzodiazepines were significant in 6. Anaerobic antibiotics and narcotic analgesics (full opioid agonists) were significant in 5, and aminoglycoside antibiotics and antidotes to hypersensitivity reactions (diphenhydramine) in 4.

DISCUSSION

We identified 9 therapeutic classes which were associated with a 2.5-fold to 5.8-fold increased risk of clinical deterioration. The results were robust to sensitivity analysis. Given their temporal association to the deterioration events, these therapeutic classes may serve as

sentinels of early deterioration and are candidate variables to combine with vital signs and other risk factors in a surveillance tool for rover teams or an early warning score.

Although most early warning scores intended for use at the bedside are based upon vital signs and clinical observations, a few also include medications. Monaghan's Pediatric Early Warning Score, the basis for many modified scores used in children's hospitals throughout the world, assigns points for children requiring frequent doses of nebulized medication.[20–22] Nebulized epinephrine is a component of the Bristol Paediatric Early Warning Tool.[23] The number of medications administered in the preceding 24 hours was included in an early version of the Bedside Paediatric Early Warning System Score.[24] Adding IV antibiotics to the Maximum Modified Early Warning Score improved prediction of the need for higher care utilization among hospitalized adults.[25]

In order to determine the role of the IV medications we found to be associated with clinical deterioration, the necessary next step is to develop a multivariable predictive model to determine if they improve the performance of existing early warning scores in identifying deteriorating patients. Although simplicity is an important characteristic of hand-calculated early warning scores, integration of a more complex scoring system with more variables, such as these medications, into the electronic health record would allow for automated scoring, eliminating the need to sacrifice

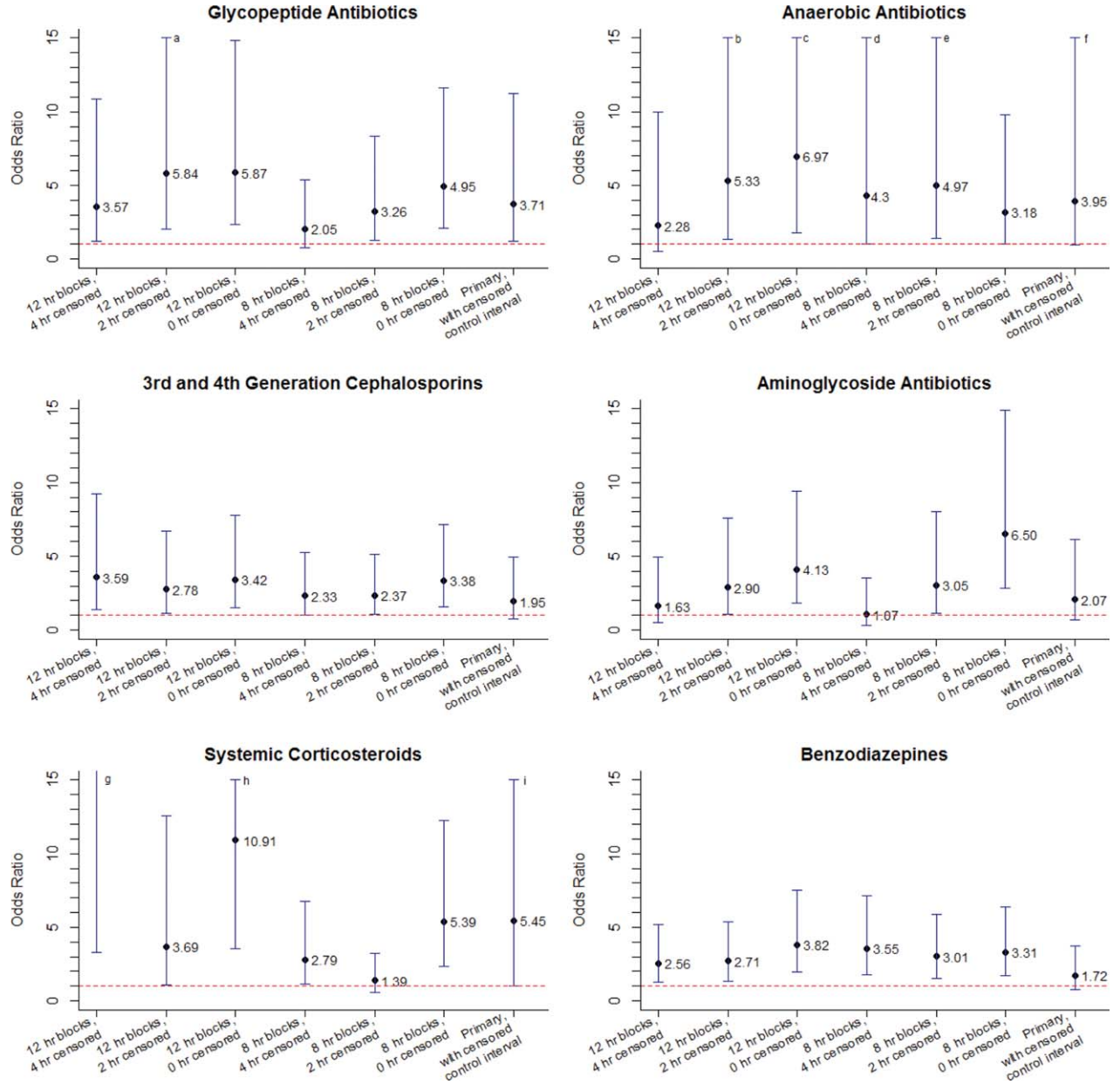

FIG. 2A. The ORs and 95% CIs for the sensitivity analyses. The primary analysis is "12 hr blocks, 2 hr censored". Point estimates with CIs crossing the line at OR = 1.00 did not reach statistical significance. Upper confidence limit extends to 16.98,[a] 20.94,[b] 27.12,[c] 18.23,[d] 17.71,[e] 16.20, [f] 206.13,[g] 33.60,[h] and 28.28.[i] The OR estimate is 26.05.[g] **Abbreviations:** CI, confidence interval; hr, hour; OR, odds ratio.

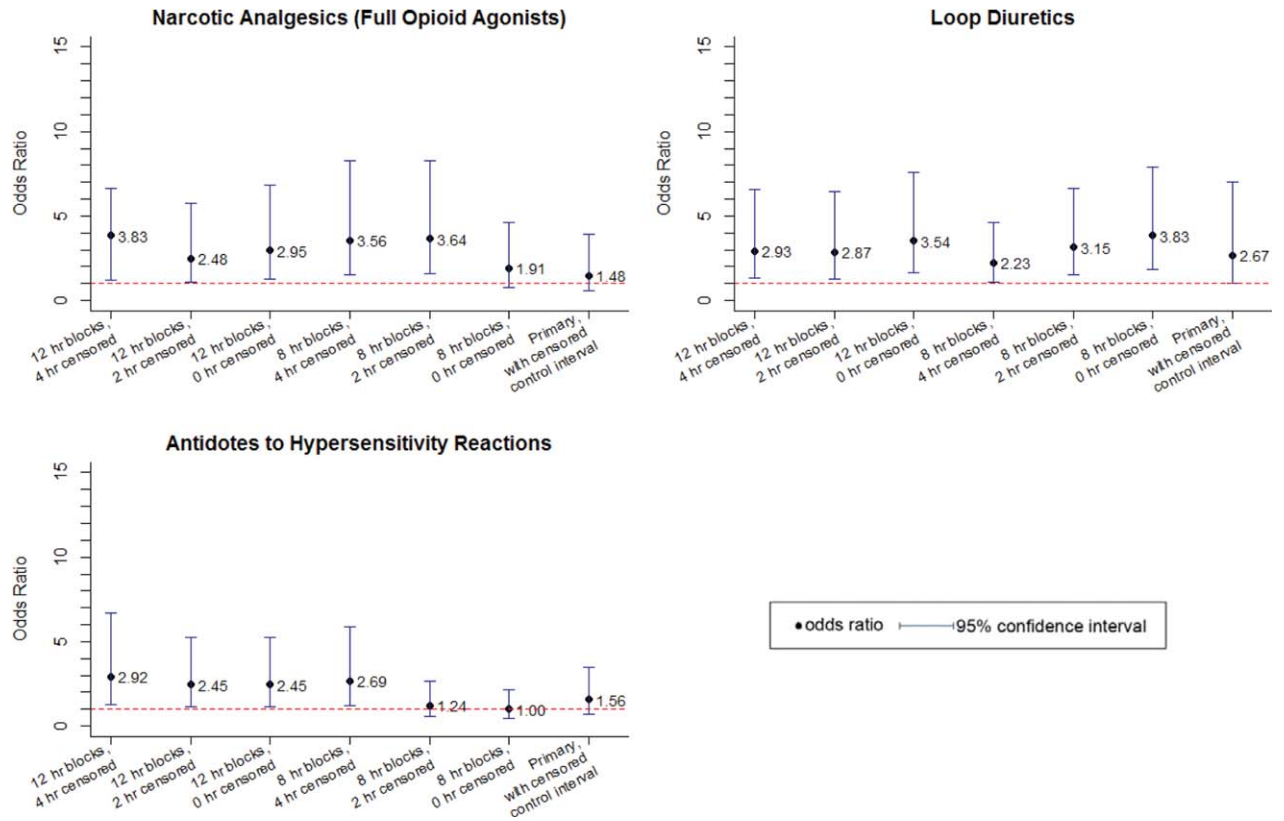

FIG. 2B. (*Continued*).

score performance to keep the tool simple. Integration into the electronic health record would have the additional benefit of making the score available to clinicians who are not at the bedside. Such tools would be especially useful for remote surveillance for deterioration by critical-care outreach or rover teams.

Our study has several limitations. First, the sample size was small, and although we sought to minimize the likelihood of chance associations by performing sensitivity analysis, these findings should be confirmed in a larger study. Second, we only evaluated IV medications. Medications administered by other routes could also be associated with clinical deterioration and should be analyzed in future studies. Third, we excluded children hospitalized for <24 hours, as well as transfers that did not meet urgent criteria. These may be limitations because (1) the first 24 hours of hospitalization may be a high-risk period, and (2) patients who were on trajectories toward severe deterioration and received interventions that prevented further deterioration but did not meet urgent transfer criteria were excluded. It may be that the children we included as cases were at increased risk of deterioration that is either more difficult to recognize early, or more difficult to treat effectively without ICU interventions. Finally, we acknowledge that in some cases the therapeutic classes were associated with deterioration in a causal fashion, and in others the medications administered did not cause deterioration but were signs of therapeutic interventions that were initiated in response to clinical worsening. Identifying the specific indications for administration of drugs used in response to clinical worsening may have resulted in stronger associations with deterioration. However, these indications are often complex, multifactorial, and poorly documented in real time. This limits the ability to automate their detection using the electronic health record, the ultimate goal of this line of research.

CONCLUSION

We used a case-crossover approach to identify therapeutic classes that are associated with increased risk of clinical deterioration in hospitalized children on pediatric wards. These sentinel therapeutic classes may serve as useful components of electronic health record–based surveillance tools to detect signs of early, evolving deterioration and flag at-risk patients for critical-care outreach or rover team review. Future research should focus on evaluating whether including these therapeutic classes in early warning scores improves their accuracy in detecting signs of deterioration and determining if providing this information as clinical decision support improves patient outcomes.

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