CHEST Original Research

ASTHMA

Budesonide Nebulization Added to Systemic Prednisolone in the Treatment of Acute Asthma in Children

A Double-Blind, Randomized, Controlled Trial

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Background: **Inhaled corticosteroids, known to be effective as a maintenance medication in chronic asthma, have also been suggested as a therapy for acute asthma when given at high doses.**

Methods: **A double-blind, randomized, placebo-controlled trial was conducted in children aged 2 to 12 years with moderate or severe acute asthma, as determined based on a clinical score of 5 to 15 points, where 15 is the most severe. We compared the addition of budesonide 1,500 μg vs placebo to standard acute asthma treatment, which included salbutamol, ipratropium bromide, and a single dose of prednisolone 2 mg/kg given at the beginning of therapy. The primary outcome was hospital admission rate within 4 h.**

Results: **A total of 906 ED visits by children with moderate or severe acute asthma were evaluated. Seventy-five cases out of 458 (16.4%) in the budesonide group vs 82 of 448 (18.3%) in the placebo group were admitted (OR, 0.84; 95% CI, 0.58-1.23; *P* = .38). However, among cases with high baseline clinical score (≥ 13), significantly fewer children were admitted in the budesonide group (27 of 76 [35.5%]) than in the placebo group (39 of 73 [53.4%]; OR, 0.42; 95% CI, 0.19-0.94; *P* = .03).**

Conclusions: **The addition of budesonide nebulization did not decrease the admission rate of children with acute asthma overall. However, it may decrease the admission rate of children with severe acute asthma.**

Trial registry: **ClinicalTrials.gov; No.: NCT01524198; URL: www.clinicaltrials.gov**

CHEST 2014; 145(4):772–778

Abbreviations: ICS = inhaled corticosteroid; LOS = length of stay

Asthma is the most common chronic disease of childhood,[1,2] and acute asthma is the most common pediatric emergency and reason for hospitalization. About 7% to 23% of patients with moderate or severe exacerbation are hospitalized.[3-5] Current guidelines recommend that patients with moderate or severe asthma exacerbation receive three doses of inhaled or nebulized β-agonist in addition to ipratropium bromide every 15 to 20 min in the first hour.[6-9] Systemic corticosteroids given early following presentation to the ED decrease the rate of admission, especially in patients with more severe exacerbation.[10]

Although several randomized controlled trials have shown clear efficacy of inhaled corticosteroids (ICSs) in the management of acute asthma as compared with placebo,[11,12] few studies have investigated the possibility of an added beneficial effect of ICSs to systemic corticosteroids.[13-16] Surprisingly, however, these pilot studies demonstrated that high-dose nebulized budesonide can acutely improve peak flow[15] and induce faster clinical improvement and hospital discharge.[14,17] Large, adequately powered studies, though, have not been performed, and a Cochrane systematic review of ICS use for acute asthma suggested further study in this area.[11]

Here, we hypothesized that adding high-dose budesonide (1,500 μg by nebulization) to the standard asthma treatment of children in the ED during the first hour would decrease their hospital admission rate. Finding that the use of high-dose inhaled budesonide, indeed, reduces hospitalization could lead to an important new treatment modality for acute asthma.

Materials and Methods

Study Design and Participants

This was a double-blind, randomized, two-arm, parallel groups, placebo-controlled clinical trial to compare the efficacy of adding nebulized budesonide (1,500 μg) or placebo (normal saline) to the treatment of children with moderate or severe acute asthma. Enrollment continued from November 2010 through March 2012. Children were eligible if they were aged 2 to 12 years, had physician-diagnosed asthma or a previous episode of shortness of breath that responded to a β_2-agonist, and had presented to the ED with moderate or severe acute asthma exacerbation. Asthma severity was determined using a clinical scoring system adopted from Qureshi et al[18] (Table 1). In this system, severe acute asthma was arbitrarily predefined as a score ≥ 12 and moderate asthma as a score from 8 to 11. Children with either mild acute asthma or severe acute asthma in critical condition requiring nonstandard immediate intervention were excluded. In addition, children with heart disease, chronic lung disease other than asthma, or those who had received systemic steroids within the past 7 days were also excluded. Patients were allowed to enroll in the study more than once. This study was conducted in accordance with the amended Declaration of Helsinki. The institutional review board at King Fahad Medical City in Riyadh, Saudi Arabia, approved the protocol (approval No. 09-102), and written informed consent was obtained from all patients' guardians.

Manuscript received September 26, 2013; revision accepted December 2, 2013.
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An abstract of this study was presented at the World Allergy Organization International Scientific Conference, December 6-9, 2012, Hyerabad, India and published in abstract form (Alangari AA, Malhis N, Mubasher M, et al. Asthma diagnosis and treatment-1012. The efficacy of budesonide in the treatment of acute asthma in children: a double-blind, randomized, controlled trial. *World Allergy Organ J*. 2012;6[suppl 1]:P12).
Funding/Support: This study was supported by a grant from the Strategic Technologies Program of the National Plan for Science, Technology, and Innovation in the Kingdom of Saudi Arabia [Grant 08-MED520-02].
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DOI: 10.1378/chest.13-2298

Outcome Measures and Sample Size Determination

The primary outcome measure was admission rate evaluated at 4 h after administration of study-assigned treatment. Secondary outcomes were change in asthma score and total length of stay (LOS) in the ED.

Sample size was deemed sufficient to detect at least a 12% differential between treatment groups in admission rate and a minimum of 90% statistical power with a two-sided 5% significance level. Additionally, sample size allowed for subgroup analysis using multiple comparisons criteria[19] to evaluate second-order interactions. The allocation of one-to-one treatment group was pursued using a permuted-block randomized scheme with variable block size.

Study Interventions

Eligible children were randomized within the pharmacy to receive three doses of budesonide solution (500 μg/dose) or placebo (normal saline). Patients also received β-agonist (2.5 mg salbutamol if patient weight was $<$20 kg or 5 mg if $\geq$20 kg) and ipratropium 250 μg/dose. Budesonide or normal saline was delivered from the pharmacy in opaque syringes and were not distinguishable from each other. Respiratory therapists, who were not involved in patients' recruitment or evaluation, mixed the delivered drug or placebo with salbutamol and ipratropium bromide. Normal saline was added to the treatment mixture to give a total volume of 3 mL/dose. They gave each patient one dose every 20 min by jet nebulization over 1 h using an age-appropriate face mask. Patients also received prednisolone 2 mg/kg po with a maximum dose of 60 mg at the beginning of the study. All participating ED physicians underwent study protocol standardization and child-enrollment training.

Assessment of Children

All children were evaluated using the asthma scoring system (Table 1) at presentation (baseline) and at 1 h and 2 h from the start of medications. Patients who remained in the ED were also evaluated at 3 h and 4 h. A decision was made to admit or discharge patients at 2, 3, or 4 h. To be discharged, the child must have had no accessory muscle use, minimal or completely resolved wheezing, and oxygen saturation $>$92%. Children who were not fit for discharge at 2-h or 3-h time points either had severe symptoms and signs and were admitted or had partially improved and so received additional salbutamol nebulizations according to their symptom severity or until they reached the 4-h time point. Discharged children were asked to continue prednisolone 2 mg/kg/d (maximum 60 mg) for 3 days in addition to β-agonist as needed and their usual maintenance medications. At 72 h postdischarge, a follow-up phone call was conducted.

Statistical Analysis

Univariate testing using χ^2 or Fisher exact or Kruskal methods were adopted to compare groups in admission rate and ED LOS at 2, 3, or 4 h, whereas *t* test and Wilcoxon methods were used to compare changes in asthma score. A multivariate statistical analysis plan allowed for the potential dependency in response due to reenrollments of a subset of children, using generalized linear mixed modeling techniques in SAS software, version 9.3 (SAS Institute Inc).[20]

Results

Description of Study Cohort

A total of 723 children were enrolled in the study, of whom 139 were allowed to reenroll and be

Table 1—*Asthma Severity Score*[18]

Variable	Asthma Score 1 Point	2 Points	3 Points
Respiratory rate, breaths/min			
Age, y			
2-3	≤34	35-39	≥40
4-5	≤30	31-35	≥36
6-12	≤26	27-30	≥31
>12	≤23	24-27	≥28
Oxygen saturation, %	>95 on room air	90-95 on room air	<90 on room air or supplemental oxygen
Auscultation	Normal breathing or end-expiratory wheezing	Expiratory wheezing	Inspiratory and expiratory wheezing, diminished breath sounds, or both
Retractions	None or intercostal	Intercostal and substernal	Intercostal, substernal, and supraclavicular
Dyspnea	Speaks in sentences or coos and babbles	Speaks in partial sentences or utters short cries	Speaks in single words or short phrases or grunts

rerandomized (105, twice; 26, three times; six, four times, and two, five times) to constitute 906 randomization assignments (458 in the budesonide group and 448 in the placebo group). Study enrollment details are displayed in Figure 1. At baseline, the overall mean ± SD asthma score was 10.63 ± 1.73, 30.9%

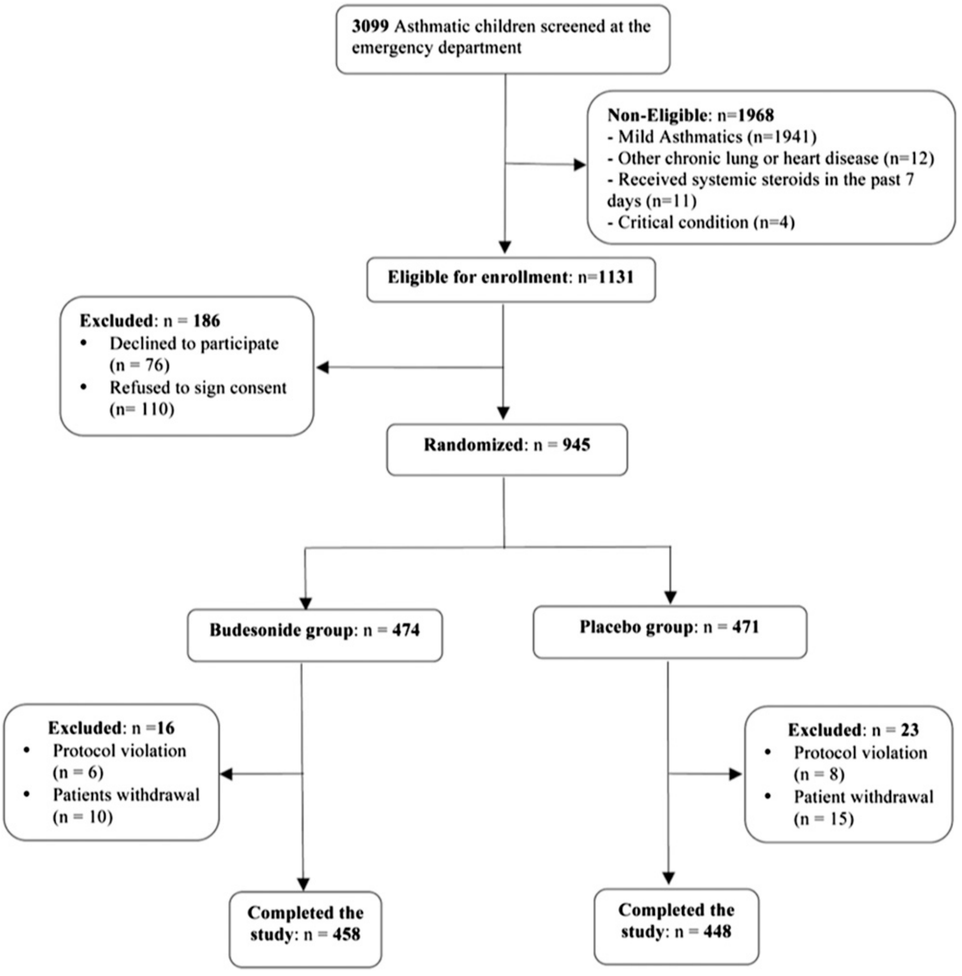

FIGURE 1. Study enrollment chart. Seventy-six subjects were excluded because they declined to participate from the beginning of the study, and 110 declined after reading the consent form, which was fully explained.

Table 2—*Comparison of Baseline Demographics and Clinical Characteristics of Budesonide vs Placebo Groups*

Baseline Characteristics	Budesonide (458) No. (%)	Placebo (448) No. (%)	*P* Value
Age, y			
2-6	305 (66.59)	310 (69.20)	.40
7-12	153 (33.41)	138 (30.80)	…
Female sex	156 (34.06)	161 (35.94)	.55
Family history of asthma			
Parental (mother, father, or both)	208 (45.41)	199 (44.42)	.76
Siblings (one or more)	328 (71.62)	301 (67.15)	.15
Smokers at home	83 (18.12)	86 (19.20)	.68
Trigger, upper respiratory infection	385 (84.06)	394 (87.95)	.09
Children with past medical history of:			
Admission to ward or PICU (lifetime)	196 (42.79)	208 (46.43)	.45
ED visits (in last year)	243 (53.06)	219 (48.88)	…
None	19 (4.15)	21 (4.69)	…
β_2-Agonist inhalations (or equivalent nebulizers) during the 6 h prior to presentation, No.			
≥5	32 (6.99)	22 (4.91)	.34
3-4	98 (21.40)	87 (19.42)	…
1-2	161 (35.15)	155 (34.60)	…
None	167 (36.46)	184 (41.07)	…
Inhaled corticosteroid prophylaxis	120 (26.20)	117 (26.12)	.98
Montelukast prophylaxis	31 (6.77)	33 (7.37)	.73

PICU = pediatric ICU.

had severe exacerbation, the mean ± SD age was 5.52 ± 2.76 years, 35% of patients were girls, and 90% had prior physician-diagnosed asthma.

Evaluation of Randomization Scheme and Interrater Reliability

Table 2 displays the groups' baseline characteristics. The table indicates lack of any significant disparities between both groups. There was no difference in the baseline asthma score as well.

Interrater reliability of scoring the severity of acute asthma was assessed using intraclass correlation. The ratings of three randomly selected physicians, out of 15 participating physicians, were assessed and compared on a pilot sample of 28 children with asthma who presented to the ED with acute asthma. The intraclass correlation coefficient was 0.85 (95% CI, 0.76-0.94). This indicated very good interrater reliability.

Evaluation of Treatment Effects

Hospital Admission: In the overall study population, 75 of 458 patients (16.4%) who received budesonide were admitted vs 82 of 448 patients (18.3%) who received placebo (OR, 0.84; 95% CI, 0.58-1.23; $P = .38$). Subgroup analysis did not indicate any statistical significance except for baseline severity with a score of ≥ 13 (severe group) vs < 13 (moderate group). Among the severe group, 27 of 76 patients (35.5%) who received budesonide were admitted vs 39 of 73 patients (53.4%) who received placebo (OR, 0.42; 95% CI, 0.19-0.94; $P = .03$). This implied a 58% reduction in the risk of admission in the budesonide group vs placebo group. Conversely, this also entailed a 2.4-fold increase in the likelihood of admission in the placebo group vs the budesonide group. Only 16.3% of patients who were randomized more than once had severe acute asthma. Their distribution was not different between the two study arms.

Asthma Score Change: There was a sustained drop in the asthma score during patients' stay in the ED in both groups, where maximum drop occurred during the first 2 h. Overall, the mean drop in asthma score from baseline to disposition was not significantly different between the budesonide group and the placebo group, with mean difference of −0.19 in favor of the budesonide group (95% CI, −0.42 to 0.04; $P = .11$). However, for the severe asthma group, this drop was significantly lower in the patients treated with budesonide vs those given placebo at disposition, with a mean difference of −0.73 (95% CI, −1.33 to −0.13; $P = .02$) (Fig 2A). In addition, the overall difference in the drop of asthma score between the two groups at 2, 3, or 4 h was not significant (Fig 2B). However, in patients with severe asthma, a steadily increasing difference in the drop of asthma score between the two study groups was noted starting from the second hour until the fourth hour, when it reached −0.87 in favor of the budesonide group (95% CI, −1.69 to −0.06; $P = .04$) (Fig 2C).

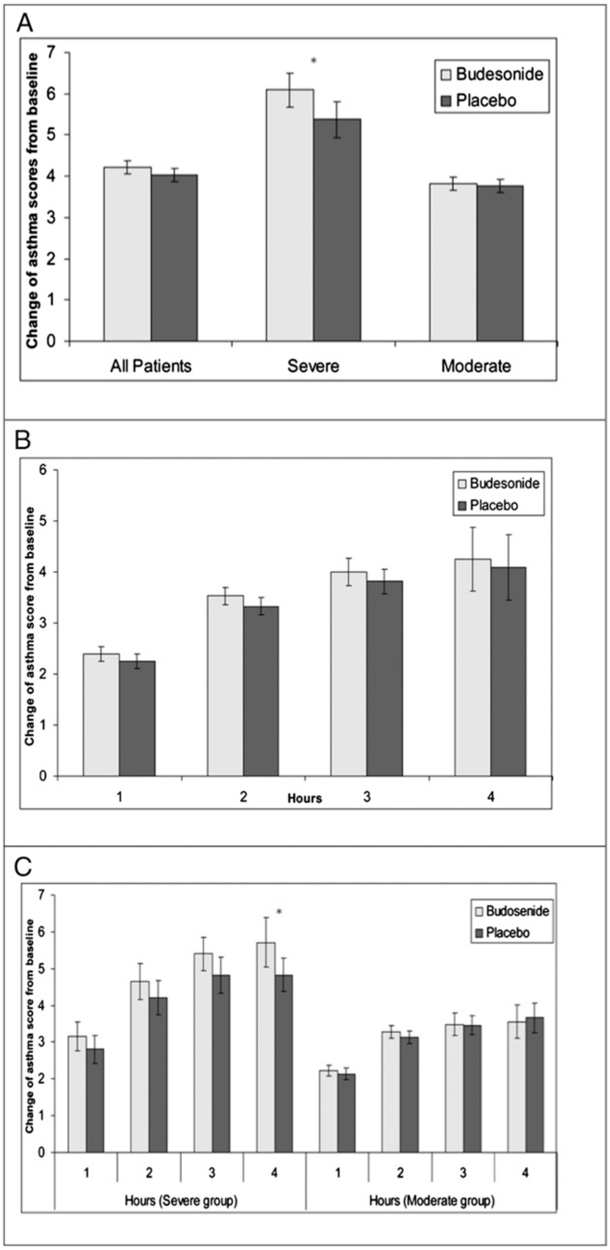

FIGURE 2. A, Mean ± 95% CI drop in asthma score from baseline in budesonide vs placebo groups at disposition time in all patients and by baseline asthma severity status. *$P = .02$ for patients with severe acute asthma. B, Mean ± 95% CI drop in asthma score from baseline in budesonide vs placebo groups (taking all patients together) at the end of each hour time point of ED length of stay. C, Mean ± 95% CI drop in asthma score from baseline in budesonide vs placebo subgroups at the end of each hour time point of ED length of stay according to baseline asthma severity. *$P = .04$ for patients with severe acute asthma at 4-h time point.

ED Length of Stay: The mean ± SD LOS in the ED was 2.79 ± 0.85 h for the budesonide group and 2.76 ± 0.84 h for the placebo group. For patients with severe asthma, the mean ± SD ED LOS was 3.36 ± 0.76 h for the budesonide group and 3.38 ± 0.79 h for the placebo group; for patients with moderate asthma, it was 2.67 ± 0.76 h for the budesonide group and 2.64 ± 0.79 h for the placebo group. None of these periods was significantly different between the two groups.

Adverse Effects: The most frequently reported adverse effects were fine tremors (17 cases) and palpitations (11 cases). None of the reported adverse effects was serious, and none was significantly different between the two groups.

Postdischarge Follow-up: Among 744 discharged cases, we were able to reach 641 cases (86.2%) by telephone 72 h postdischarge. In 606 cases (94.5%), improvement was reported, while 35 cases (5.5%) needed an unscheduled visit to a health-care facility. Among those, eight patients were admitted to the hospital (three in the budesonide group and five in the placebo group) and 27 were treated in the ED, then discharged (16 in the budesonide group and 11 in the placebo group). There was no statistically significant difference between the two groups in their outcome at 72 h postdischarge.

Discussion

To our knowledge, the largest trial among the very limited number of randomized and blinded studies that have previously examined the addition of ICSs to systemic steroids in the treatment of acute asthma in the ED was by Upham et al.[16] They studied 180 children with moderate to severe acute asthma and gave budesonide 2 mg in two divided doses. Using the same asthma score that we used, they found no difference in the admission rate, asthma score, and ED LOS between the two study arms, which is consistent with our findings in the overall study population. However, when we examined patients with severe acute asthma (score ≥ 13), we found a significantly lower admission rate and more drop in the asthma score in the budesonide group. In more practical terms, up to seven patients would need to be treated with budesonide to save one admission as compared with placebo. This would highly be cost effective, since 1-day admission of a patient with severe acute asthma in our institution costs around $500 per night, while three doses of budesonide (500 μg/dose) costs about $7. This observation needs further study. The advantage of ICS in patients with severe acute asthma, as compared with moderate acute asthma, has been suggested in previous studies.[21-23] Additionally, giving ICS to patients with acute asthma carries an educational message about continuing ICS during these episodes. The adverse effects reported in our study are likely to be due to the β-agonist.[11]

A significant beneficial effect of high-dose ICS in this setting is counterintuitive, since potent systemic corticosteroids were used in all patients.[24] However, ICSs were shown to act earlier than systemic corticosteroids. For example, a significant decrement in sputum eosinophils was reported in patients with asthma after 2 h of the administration of inhaled fluticasone as compared with oral prednisone.[25] Moreover, a reduction in airway responsiveness to adenosine 5′-monophosphate was demonstrated within 2 h after a single inhalation of fluticasone.[26] Such effects were presumed to be due to the topical nongenomic vasoconstrictor action of ICS.[27,28] Based on the clinical efficacy and pharmacokinetics of ICS, it would be reasonable to speculate that using an equivalent dose of a different ICS administered by pressurized metered-dose inhaler would have a similar effect.[29-31]

In another interesting observation, we noticed that the relationship between the rate of admission and the patients' scores was not linear. In other words, if we consider the asthma severity score range from 8 to 15, we find that, on average, a one-point drop in the score decreases the likelihood of admission by 2.6-fold; looking only at scores ≥ 13, however, a one-point drop will decrease likelihood of admission by 4.1-fold. This has to be kept in mind when interpreting changes in the asthma score.

There are several limitations to our study. Our positive results relative to children with severe acute asthma need to be interpreted with caution because they were based on subgroup analysis, even though common confounders were taken into account when performing statistical analysis. Also, the definition of severe acute asthma was a score of ≥ 12 according to the original score design, but our significant results were only demonstrated in patients with a score ≥ 13. The point of distinction between severe and moderate exacerbation in the asthma score is arbitrary, nevertheless. We realize, however, that this was not a predefined point, giving another reason for cautious interpretation. Moreover, the reenrollment of some subjects that was undertaken to increase the number of cases within our study time limitation could have introduced selection bias. This issue was taken into consideration, however, during the statistical analysis by using the generalized linear mixed modeling technique, and the randomization balance was maintained. In addition, we attempted to measure the peak expiratory flow rate in children > 7 years old, but, unfortunately, only very few reliably performed the test. This was not so surprising,[32] especially because most of the patients were not pretrained to do it. Another limiting factor is that this is a single-center study, which may limit the generalizability of results.

In conclusion, our study did not show beneficial effect of the use of high-dose ICSs as add-on therapy to the current regimen in the treatment of moderate to severe acute asthma in the first hour in the ED, but suggests a possible benefit in severe acute asthma.

Acknowledgments

Author contributions: Dr Alangari had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Dr Alangari: contributed to conception and design of the study; interpretation of data; and writing, review, and approval of the latest version of the manuscript and served as principal author.
Dr Malhis: contributed to study design and supervision, acquisition of data, and review and approval of the latest version of the manuscript.
Dr Mubasher: contributed to data analysis, writing the statistical section of the manuscript, and review and approval of the latest version of the manuscript.
Dr Al-Ghamedi: contributed to study design, drug dispensing, and review and approval of the latest version of the manuscript.
Dr Al-Tannir: contributed to study design, data management, and review and approval of the latest version of the manuscript.
Mr Riaz: contributed to data analysis and review and approval of the latest version of the manuscript.
Dr Umetsu: contributed to study design, manuscript preparation, and review and approval of the latest version of the manuscript.
Dr Al-Tamimi: contributed to study design, supervision of data collection, and review and approval of the latest version of the manuscript.
Financial/nonfinancial disclosures: The authors have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.
Role of sponsors: The sponsor had no role in the design of the study, data collection, or data analysis.

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