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Theophylline in Acute Childhood Asthma: A Meta-Analysis of Its Efficacy

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Summary. Although theophylline is a widely used drug for the treatment of acute childhood asthma, its efficacy has not been clearly established. This study constitutes a meta-analysis of published randomized clinical trials of theophylline in children hospitalized with acute asthma. We conducted a search of English language MEDLINE citations from 1966 to 1995 and analyzed the methods of each report meeting study criteria. We pooled similar clinical measures across studies if a test for homogeneity of effect size was non-significant. The six methodologically acceptable randomized clinical trials included a total of 164 children less than 18 years of age. Incomplete reporting of measures and variances was common. No study included children in intensive care settings. Using pooled results, pulmonary function parameters [forced expired volume in 1 second (FEV_1), forced expired flow (FEF)] appeared better at 24 hours in the theophylline group, but the results did not reach statistical significance (mean effect difference, +3.9% predicted values; pooled effect size, +1.6 SDS; $P = 0.25$). A mean of 2.1 more albuterol treatments were administered in the theophylline group (pooled effect size, −0.18 SDS; $P = 0.02$), and the mean hospital stay was slightly longer (mean effect difference, −0.31 days; pooled effect size, −0.18 SDS; $P = 0.03$). We conclude that currently available data do not indicate a significant beneficial effect of theophylline in children hospitalized with acute asthma. There is evidence for weak detrimental effects. Theophylline efficacy in intensive care unit settings remains unstudied. **Pediatr Pulmonol. 1996; 21:211–218.** © 1996 Wiley-Liss, Inc.

Key words: Asthma, theophylline, children, meta-analysis.

INTRODUCTION

Theophylline is a methylxanthine bronchodilator widely used for the treatment of acute and chronic asthma in children. In 1991, the National Heart, Lung, and Blood Institute issued guidelines that recommended theophylline as part of the pharmacologic management of children hospitalized with acute asthma.[1] Other authors have also suggested its use at the time of admission or when a child with asthma faces impending respiratory failure.[2–7] Despite these recommendations, there are few randomized clinical studies evaluating theophylline efficacy in children. A 1988 meta-analysis of 13 clinical trials failed to "support or reject" the use of theophylline in severe asthma exacerbations,[8] although only one of the trials reviewed included children.[9] While four recent trials have failed to demonstrate the efficacy of theophylline for acute asthma,[10–13] the small sample sizes limit the power of these studies to detect drug effects.[14] Clear evidence of therapeutic efficacy in children is particularly important given the risk of theophylline toxicity.[4,15–17]

The purpose of this paper is to review systematically the published randomized clinical trials of theophylline efficacy in children hospitalized with acute asthma. Meta-analysis[18] is used for pooling results across studies when appropriate. This statistical method greatly increases the power to detect treatment effects, particularly if null effects were observed in the individual studies because of inadequate sample size. Essential elements are also proposed in the design and reporting of future clinical trials to strengthen the inferential power.

MATERIALS AND METHODS

We considered the *efficacy* of theophylline to pertain only to its effects in the context of standard therapy for

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asthma, including other bronchodilators and steroids. While theophylline may be beneficial as a sole agent compared with a placebo, we did not address this possibility since it would have no relevance for clinicians currently treating acute asthma.

Literature Review and Abstraction

We searched the MEDLINE on-line database for the period 1966 through May 1994 to find all English language articles indexed for the subjects *theophylline* and *asthma.* The following search language was used:

> (aminophylline (mh) *or* theophylline (mh)) and (asthma (mh) or bronchial spasm (mh)) *and* not foreign (la)

This search found 1,854 citations. As a test of the sensitivity of the search strategy, we compared the citations with Littenberg's[8] list of studies used in his 1988 meta-analysis of aminophylline. All the citations used in Littenberg's analysis were found by our MEDLINE search strategy without searching additional bibliographies.

Articles were excluded for the following reasons: 1) the article was not a randomized clinical trial of theophylline or aminophylline with a concurrent control group; 2) the subjects did not have acute asthma requiring admission to the hospital; or 3) the results were not reported separately for subjects less than age 18 years. We also reviewed the citations within each eligible article but did not find any additional eligible studies. Five studies initially met the criteria for inclusion in these analyses. The search was updated in February 1995 and an additional clinical trial was found.[13] Although our exclusion criteria limited the analyses to children with hospitalized acute asthma, we did not find additional randomized clinical trials of acute asthma in other clinical settings, such as emergency departments.

All data pertaining to the studies' methods were abstracted by the primary author (D.C.G.). In two studies,[9,19] the authors provided only a graphical representation of the results, so the numerical values of the outcome measures were determined from the figures. Since this was a review of efficacy, we did not analyze the data on adverse effects.

Analysis

For each reported outcome we determined the *effect difference* (the difference between the mean or median value for the theophylline and the control groups) and the *percent effect difference* (the percent difference between the mean or median value for the theophylline and the control groups). An effect was assigned a positive value if the theophylline group benefited. We also calculated a measure of the difference between the groups standardized by the variance, termed the *effect size.* The effect size is equal to the effect difference divided by the standard deviation.[18] The use of effect sizes allows for comparisons across different studies when units of measurement vary. We tested for the homogeneity of effect sizes with a χ^2 test and if significant heterogeneity ($P > 0.05$) was not present, calculated pooled effect size using the methods described by Light and Pillemer.[18] Weighted *coefficients of variation* (CV = standard deviation/mean) were calculated for the total sample by weighting CV in each treatment group by group sample size.

RESULTS

The six published clinical trials evaluating theophylline for the treatment of children hospitalized with acute asthma included a total of 164 subjects ranging in age from 1.5 to 18 years.[10–13] The methods for each study are summarized in Table 1. All the studies randomly allocated patients to treatment or comparison groups with double blinding. Patients in the treatment groups received either an intravenous (IV) theophylline or aminophylline bolus followed by continuous infusion. In five studies the control groups received IV saline or dextrose solution[9–11,13,19] and in one study they received IV albuterol.[19] All patients received IV corticosteroids with a methylprednisolone dose-equivalence ranging from 2.2 to 8.3 mg/kg in the first 24 hours. In five of the six studies, serum theophylline levels were monitored.[9–13] Sample size calculations were presented in only two studies.[10,13]

Individual Reports

The first clinical trial of theophylline for children with acute asthma is also the only trial that shows a statistically significant effect favoring theophylline ($P < 0.05$).[9] In 1971, Pierson et al.[9] randomly allocated 23 children with acute asthma who had failed to respond to three doses of subcutaneous epinephrine to receive either IV aminophylline or saline. Both groups were treated with nebulized isoproterenol and phenylephrine, in addition to IV corticosteroids, fluids, and antibiotics. At 24 hours, the effect difference of the forced expired volume in 1 second (FEV_1) was +15.7% (units are percent of predicted values) and 10.9% for the forced vital capacity (FVC) (Table 2). The low variances in Pierson et al.'s[9] data are reflected in the large effect sizes of +3.6 SD for FEV_1 and +2.1 SD for FVC. The clinical score ("Pulmonary Index") was not reported beyond "improvement" in the aminophylline-treated group.

In 1979, Hambleton and Stone[19] compared IV aminophylline to very-low-dose IV albuterol (4 μg/kg bolus, then 0.6 μg/kg/hr) in 18 children; both groups received

TABLE 1—Selected Characteristics of Methods in Clinical Trials of Theophylline in Children Hospitalized With Acute Asthma[1]

Study	Age in yr (mean)	Total sample size[2]	Entry criteria	Study duration (hr)	Treatment group	Comparison group	Comments
Pierson et al.,[9] 1971	5–17 (12)	23	Failed ER treatment with epinephrine SQ × 3 doses	24	IV aminophylline IV corticosteroids IV antibiotics Nebul. phenyl-epherine and isoproterenol	Placebo IV corticosteroids IV antibiotics Nebul. phenyl-epherine and isoproterenol	Aminophylline dose not specified Medications prior to study vary between groups
Hambleton et al.,[19] 1979	1.5–7 (NR)	18	"... sufficiently ill to require intensive hospital treatment on clinical grounds"	24	IV aminophylline IV corticosteroids	IV albuterol IV corticosteroids	Number of subjects in treatment and comparison groups not listed
DiGiullio et al.,[11] 1993	2–18 (7)	29	Failed ER treatment with nebulized albuterol × 3 doses	Until discharge	IV theophylline Nebul. albuterol q 2–4 h (per treating physician) IV corticosteroids	Placebo Nebul. albuterol q 2–4 h (per treating physician) IV corticosteroids	8 AM–11 PM admissions only Excluded if patient required intensive care Five patients withdrawn
Carter et al.,[12] 1993	5–18 (12)	21	Failed ER treatment with nebulized albuterol × 3 doses	36	IV aminophylline Nebul. albuterol q 20 min–6 h (per FEV_1) IV corticosteroids	Placebo Nebul. albuterol q 20 min–6 h (per FEV_1) IV corticosteroids	Excluded for $PaCO_2 \geq 50$ mm Hg, impending respir. failure, chronic illness, or unable to perform PFT Four patients withdrawn
Strauss et al.,[10] 1994	5–18 (11)	31	Failed ER treatment with nebulized albuterol × 3 doses	Until discharge	IV aminophylline Nebul. albuterol (frequency per treating physician) IV corticosteroids	Placebo Nebul. albuterol (frequency per treating physician) IV corticosteroids	Excluded if patient had non-asthma chronic disease, or if needed intensive care
Needleman et al.,[13] 1995	2–18 (8)	42	Failed ER treatment with nebulized albuterol × 3 doses	Until discharge decision	IV aminophylline Nebul. albuterol frequency per treating physician) IV corticosteroids	Placebo Nebul. albuterol (frequency per treating physician) IV corticosteroids	Excluded if taking theophylline, presence of cardiac disease, or if needed intensive care Three patients withdrawn

[1]All studies used double-blinded random allocation to treatment or comparison group. NR, not reported; ER, emergency room; SB, subcutaneous; Nebul., nebulized.
[2]Excludes subjects who were withdrawn from study.

TABLE 2—Measured Outcomes in Clinical Trials of Theophylline in Children With Acute Asthma[1]

Study	Time (hr)	Theophylline group (SD)	Comparison group (SD)	Effect difference[2]	Effect size[3] (SD units)	Comment
Pierson et al.[9] (n = 23)						
FEV_1 (% of predicted)[4]	24	77.1 (±3.9)	61.4 (±4.9)	+15.7	+3.6	
FVC (% of predicted)[4]	24	75.9 (±5.3)	65 (±5.3)	+10.9	+2.1	
Clinical index	NR	NR	NR	—	—	". . . improvement . . ."
PaO_2	NR	NR	NR	—	—	"Too few had serial PaO_2 to make the data statistically valid"
Hambleton et al.[19] (n = 18)						
Clinical scores[4]	24	15.5 (NR)	15.5 (NR)	0	0	
Respiratory rate (per min)[4]	24	33 (NR)	33 (NR)	0	0	
Pulse rate (per min)[4]	24	112 (NR)	125 (NR)	+13	—	
DiGiulio et al.[11] (n = 29)						
Hours to achieve clinical score of 2	—	30.4 (±16.8)	27.0 (±10.3)	−3.3	−0.2	
Number of albuterol treatments	Discharge	8.4 (±6.1)	7.4 (±5.1)	−1.0	−0.2	
Hours of supplemental O_2	—	27.6 (NR)	27.6 (NR)	0	0	15 subjects required O_2; data collected on 9
Change in clinical score	24	3.6 (±1.9)	3.7 (±2.4)	+0.1	+0.1	
Carter et al.[12] (n = 21)						
FEV_1 (% of predicted)[4]	24	64 (±22%)	54 (±12%)	+10	+0.6	
Rate of improvement of FEV_1	—	NR	NR	—	—	". . . no significant differences . . ."
Clinical score (median)[4]	24	1.5 (NR)	2.1 (NR)	−0.6	—	
No. of albuterol nebulizations	36	20 (±19)	15 (±6)	−5	−0.4	
Total dosage of albuterol (mg)	36	83.5 (±88)	67.5 (±40)	−16	−0.2	
Hospital stay (days)	—	3.5 (±2.5)	3.0 (±1.5)	−0.5	−0.2	
Strauss et al.[10] (n = 31)						
PEFR (% of predicted)	24	53 (±21)	67 (±22)	−14	−0.7	
Albuterol treatments	24	6.14 (±1.16)	6.00 (±0.71)	−0.14	−0.1	
Hospital stay (days)	—	2.58 (±1.5)	2.33 (±1.3)	−0.25	−0.2	
Needleman et al.[13] (n = 42)						
Clinical score	24	3.05 (±3.25)	2.38 (±2.19)	−0.67	−0.2	
Hospital stay (days)	—	2.17 (±1.33)	2.00 (±1.13)	−0.17	−0.1	

[1]Mean values listed unless otherwise indicated. Values in parentheses indicate standard deviation. Positive sign of effect difference signifies that aminophylline group had a better outcome. Sample size is the number of subjects listed by author for the entire study; not all subjects had measurements for every outcome (see Table 3). NR, not reported.
[2]Effect difference is difference in means of theophylline and comparison group (expressed in units of measurement).
[3]Effect size is the effect difference divided by the standard deviation (expressed in units of standard deviations).
[4]Determined from figure in paper.

IV corticosteroids. At 24 hours, the mean clinical scores and respiratory rate were not ". . . statistically . . ." different. The mean values are presented in a figure but without any measure of the variance or the sample size of each group. These limitations prevented us from pooling the study results.

The next four clinical trials shared similarities in design. The primary inclusion criterion was failure of emergency room treatment with three doses of nebulized albuterol. Patients requiring intensive care or with impending respiratory failure were excluded. To maintain blinding, sham "theophylline levels" were reported for the placebo group patients along with actual levels for the treatment group by an investigator not involved in assessing outcomes. DiGiullio et al.[11] studied 29 children and found small effect differences that were not statistically significant. The theophylline group on average needed 3.3 more hours than the control group to achieve a low clinical score (effect size, −0.2 SD), and the theophylline group had one additional albuterol treatment by the time of discharge (effect size, −0.2 SD). The percent effect differences were 13% and 14%, respectively. The duration of supplemental oxygen was identical. The difference in clinical score at 24 hours was 0.1 (effect size, +0.1 SD), favoring the theophylline group. Carter et al.[12] studied 21 patients; they observed that the theophylline group had consistently greater FEV_1 values (percent of predicted value) then the comparison groups from study entry through study completion at 36 hours. The effect difference was +10% (percent of predicted) (effect size, +0.6 SD) at 24 hours and was not statistically significant. The median clinical score was 29% lower in the theophylline

TABLE 3—Pooled Results From Four Studies Comparing the Effect of Theophylline With Placebo in Acute Childhood Asthma[1]

Measure	Degrees of freedom	Test of homogeneity (χ^2)[2]	Mean effect difference[3]	Pooled effect size[2,4] (95% confidence intervals)	*P* value
FEV_1 or PEFR[9,10,12]	2	1.2*	+3.9% of predicted	+1.6 SD (−2.6, +5.9)	0.25
Albuterol treatments[10–12]	2	<1*	−2.1 treatments	−0.18 SD (−0.3, −0.1)	0.02
Hospital stay[10,12,13]	2	<1*	−0.31 days	−0.18 SD (−0.3, −0.05)	0.03

[1]Positive effect difference signifies that aminophylline group had a better outcome. SD, standard deviation units.
[2]From Ref. 18.
[3]Effect difference is difference in means of theophylline and comparison group (expressed in units of measurement).
[4]Effect size equals effect difference divided by the standard deviation.
*$P > 0.05$.

group, but the variance was not reported. The theophylline group received five more albuterol treatments by 36 hours (effect size, −0.4 SD) and required a half-day longer hospital stay (effect size, −.0.2 SD) than the control group. Strauss et al.[10] enrolled 31 children age 5–18 years. The children in the theophylline group had poorer outcomes in all three clinical measures [peak expiratory flow (24 hours), number of albuterol treatments, and length of hospital stay] although none were statistically significant. The effect difference was −14% for PEFR (effect size, −0.7 SD), −0.25 days for hospital stay (effect size, −0.2 SD), and −0.14 for the number of albuterol treatments by 24 hours (effect size, −0.1 SD). Needleman et al.[13] included 45 children ranging in age from 2 to 18 years. For the two outcomes presented, the theophylline group had poorer outcomes, but differences were not statistically significant. The effect difference was −0.67 for the clinical score (effect size, −0.2 SD) and −0.17 days (effect size, −0.1 SD) for the hospital stay.

Pooled Analysis

Pooling of results across studies was limited by the dissimilar outcomes and the failure to report results and variances quantitatively. Three parameters were reported in more than one study—FEV_1 or peak expiratory flow rate (PEFR) at 24 hours, the number of albuterol treatments, and the length of hospital stay. We used the effect size for pooling since it is a measure of the effect difference standardized by each study's variance. The test for homogeneity of effect for each parameter did not detect significant differences (Table 3). Therefore, the effect sizes were pooled and 95% confidence intervals calculated. The pooled effect size of the 24 hour spirometry measure (FEV_1 or PEFR) was +1.6 SD (95% confidence interval, −2.6, +5.9) with a *P* value of 0.25 (Table 3). For the number of albuterol treatments, the pooled effect size was −0.18 SD (95% CI, −0.3, −0.1). While this effect was statistically significant ($P = 0.02$), it should be noted that the mean effect difference of 2.1 more treatments in the theophylline group compared with the control group is small. Similarly, the pooled effect size of −0.18 SD (95% CI, −0.3, −0.05) for hospital stay was statistically significant ($P = 0.03$), but this represented an average longer hospital stay in the theophylline group of only 0.31 days.

Sample Size Calculations

We also determined for each outcome measure in each study the total sample size necessary to detect a 20% effect difference with an α of 0.05 (two-tailed) and a power of 0.80.[20] These parameters represent a minimal sample size for a clinical trial with a moderate chance of a Type I or II error. Reducing the chance of these errors further or detecting a smaller effect difference would require a larger sample size. The minimal difference between treatment and control groups that is large enough to consider the efficacy of theophylline clinically relevant is arguable. We chose a 20% effect as a difference that would seem important for all the outcome measures used in the studies under review. Table 4 shows the sample size required using the variances found in each study's outcome measure. These sample sizes demonstrate the extent to which the clinical trials were "underpowered," with the exception of Pierson et al.'s[9] trial, which observed very low variances in spirometric parameters compared with other studies.[10,12]

DISCUSSION

Acute asthma continues to be one of the most common causes of pediatric hospitalization, with 187,000 admissions in 1991.[21] Clinicians frequently prescribe theophylline or aminophylline to treat these children,[22,23] yet the six randomized clinical trials of this drug have included only 164 children. The results from our meta-analysis of these trials indicates with a high degree of certainty that any beneficial effects on pulmonary function are slight, if present at all. There is also evidence suggesting detri-

TABLE 4—Sample Size Required to Demonstrate a 20% Effect Difference Between Aminophylline and Comparison Group[1]

Study	Effect difference	% Effect difference	Sample size used theophylline/ controls	Total required sample size to detect 20% effect difference[2]
Pierson et al.[9]				
FEV_1 (% of predicted)	+15.7	26	11/12	4
FVC (% of predicted)	+10.9	15	11/12	6
Digiiulio et al.[11]				
Hours to achieve clinical score of 2	−3.3	13	16/13	198
Number of albuterol treatments (by discharge)	−1.0	14	16/13	449
Change in clinical score	+0.1	3	16/13	265
Carter et al.[12]				
FEV_1 (% of predicted)	+10	19	12/9	85
No. of albuterol nebulizations (by 36 hr)	−5	33	12/9	544
Total dosage of albuterol (mg; by 36 hr)	−16	24	12/9	705
Hospital stay (days)	−0.5	17	12/9	348
Strauss et al.[10]				
PEFR (% of predicted)	−0.14	21	9/14	81
Albuterol treatments (by 24 hr)	−0.14	2	9/14	20
Hospital stay (days)	−0.25	11	11/15	283
Needleman et al.[13]				
Clinical score	−.67	28	22/20	1024
Hospital stay (days)	−.17	9	22/20	297

[1]Fractions are rounded up. Assumes a two-tailed α of 0.05 and 80% power ($\beta = 0.20$). Positive effect difference signifies that the aminophylline group had a better outcome. Measures reported without standard deviations were excluded.

[2]$N = [(1/q_1 + 1/q_2)\ S^2\ (Z_\alpha + Z_\beta)^2]/E^2$ (see Ref. 20) where:

q_1 = proportion of subjects in group 1
q_2 = proportion of subjects in group 2
S = standard deviation
Z_α = the standard normal deviate for α [$Z_\alpha = 1.96$ when $\alpha = 0.05$ (two-tailed)]
Z_β = the standard normal deviate for β ($Z_\beta = 0.84$ when $\beta = 0.20$)
E = expected effect size

mental effects, as measured by the greater number of albuterol treatments required and the longer hospital stays. Intravenous theophylline for acute childhood asthma remains, therefore, an unproven therapy.

Limitations of Pooling Results

These analyses are limited by the dissimilarities in the treatments prescribed and the outcomes reported by the investigators. We included the PEFR results from Strauss et al.[10] because this measure correlates highly with the FEV_1.[24] A more difficult decision was whether to pool the data of Pierson et al.[9] This single trial has been the sole evidence to support theophylline use for the past two decades. Pierson et al.'s[9] trial differs from the others in three important respects: the pulmonary function standard deviations are low compared with the other published trials; the study used medications that are no longer in wide use (nebulized isoproterenol and phenylephrine); and the dose of corticosteroid was the lowest of the studies. The apparent efficacy observed by Pierson et al.[9] could suggest that theophylline is more beneficial when less efficacious concurrent medications are used. This possibility seems unlikely since the lack of efficacy of theophylline in adults is not sensitive to the concurrent medication regimen.[8] Exclusion of Pierson et al.'s[9] trial from our analyses would not have altered our findings.

Research Implications

While results from the four recent clinical trials failed to demonstrate theophylline efficacy in hospitalized children, interest remains high for its use in critically ill patients.[25] To date, there have been no published studies of theophylline effects in children with respiratory failure. The utility of future studies will depend on four design characteristics: the outcome criteria selected for study, adequate study power, the population selected, and the reporting of the results. The results from our analysis underscore the importance of carefully considering the relevance of outcome measures.[26,27] For critically ill patients, improvement in physiologic parameters is generally easy to measure. Equally important are outcomes meaningful to patients and their families—the likelihood of intubation, the number of intensive care unit days, and the overall hospital length of stay.

Our systematic review provides future researchers with guidance in estimating the necessary sample size. Investi-

gators need to judge the smallest effect considered meaningful by clinicians and families. The effect differences observed for most of the outcome measures in the published theophylline trials were small and would require a relatively large sample size to detect. In addition, the variance associated with each outcome must be accurately estimated or the trial is likely to be "underpowered." Historical data from a hospital can be helpful to estimate variance for some outcomes, such as the length of stay or the number of albuterol treatments. Pilot data under study conditions are more likely to provide an accurate estimate and are essential for pulmonary function parameters or for a clinical score. Future investigators should also consider the generalizability of the study population. The hospitalization rate for acute asthma is highest in children under age 5 years,[28] the age group least represented in previous trials. There are also large differences in hospitalization rates by gender and race; adequate representation of these patient groups will ensure that study results are applicable to a broad clinical population.

Finally, this review demonstrates the importance of full and clear reporting of methods and results. Incomplete reporting of methods or data, by omitting either a quantitative measure altogether or its variance, hinders a reader's ability to judge the studies' validity. In turn, incomplete reporting is an unnecessary barrier to meta-analysis. Reporting of each subject's outcome measures is particularly desirable for small trials in which the data are less likely to have a normal distribution, thus necessitating nonparametric tests.

Is it feasible to conduct future trials of theophylline efficacy? The small number of existing studies and their small sample size suggest that there are substantial barriers to conducting these trials. At the same time, new therapies are being developed that may reduce theophylline's potential role even further. The positive and negative effects of theophylline seen in this meta-analysis may be statistically significant in future trials with large sample sizes, but their relevance may still be questionable unless larger effect differences are observed.

Clinical Implications

Clinicians caring for children with acute asthma must still make therapeutic decisions with uncertain knowledge about the effects of theophylline. For children in non-intensive care settings, the pooled results indicate that theophylline adds little to corticosteroids and nebulized albuterol. Children receiving theophylline appear to have slightly longer hospital stays and receive more albuterol treatments. Even assuming there are no detrimental effects on a patient's clinical course, adverse reactions to intravenous theophylline can include rare life-threatening events, and administration requires blood drawing to determine serum levels. These are additional factors to consider in the decision to use theophylline until further data become available. For critically ill children, intravenous theophylline remains an unstudied treatment. Routine use is controversial when one considers the lack of evidence indicating benefits; there is some evidence indicating worse outcomes in non-intensive care patients. Randomized clinical trials of theophylline for children with respiratory failure should be undertaken before intravenous theophylline is accepted in the treatment protocols in intensive care settings.

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