Evidence Table 18. Managing Exacerbations: IV Aminophylline

Abbreviations used in table:

CI	**confidence interval**
FEV_1	**forced expiratory volume in 1 sec.**
IV-A	**intravenous aminophylline**
OR	**odds ratio**
P	**placebo**
PEFR	**peak expiratory flow rate**
PICU	**pediatric intensive care unit**
SMD	**standardized mean difference**
WMD	**weighted mean difference**

*** indicates primary outcome**

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Citation (Sponsor)	Study Design	Purpose/Objective	Study N (Number Evaluable)	Population Characteristics	Asthma Severity at Baseline (if reported)	Treatment	Dose	Lung Function	Severity/Admissions	Safety
Parameswaran et al. Addition of intravenous aminophylline to beta$_2$-agonists in adults with acute asthma. Cochrane Database Syst Rev 2000;(4):CD002742. (NHS Research and Development UK)	Meta-analysis of randomized, controlled trials published between 1971 and 1999	To determine whether intravenous aminophylline (IV-A) has an additional bronchodilation effect in adult patients with acute asthma when used in conjunction with inhaled beta-agonists with or without corticosteroids (intravenous, oral, and/or inhaled)	Fifteen trials, 11 from the United States and one each from Australia, the United Kingdom, Uruguay, and Malaysia, yielding 17 trial comparisons. All were published between 1979 and 1994. Overall methodological quality was moderate (mean Jadad score of 3.1); concealment of allocation adequate in 7 trials. Only three trials had sample sizes larger than 30 subjects/group.	Age ≥18 yr although two studies included subjects >15 yr and two >16 yr; upper limit ranged from 45 to 60 yr Gender Not reported	Acute asthma or acute exacerbation of asthma and previous diagnosis of asthma Airflow limitation described as severe in 11 trials as defined by PEFR (<40% predicted or 150 L/min) or FEV$_1$ (<40% predicted or 1 L). Studies conducted in emergency departments	Arm 1 IV-A plus generic beta-agonists (n=353) Arm 2 Standard care (P) (n=386)	Five trials used epinephrine, 5 salbutamol, 3 meta-isoproterenol, 2 isoproterenol, and 2 albuterol as concomitant beta-adrenergic agonists. Five trials used hydrocortisone, and 4 used methylprednisolone as corticosteroid cointervention.	*There was no difference in PEFR or FEV$_1$ between groups at any time period studied. At 12 hours post infusion, both PEFR (WMD 8.3 L/min, 95% confidence interval (CI) –21 to 37; WMD 2.2% predicted, 95% CI –6 to 11) and FEV$_1$ (WMD 0.4 liter, 95% CI –0.2 to 1.0; WMD 4.3% predicted, 95% CI –18 to 27) failed to demonstrate a difference. There was no difference at 24 hours for PEFR (WMD 22.2 L/min, 95% CI –57 to 101; WMD 6.4% predicted, 95% CI –7 to 20) or FEV$_1$ (WMD 0.4 liter, 95% CI –0.1 to 1.0; WMD 4.4% predicted, 95% CI –17 to 25).	Hospital admission was slightly lower but not significant in IV-A vs. P (odds ratio (OR) 0.58, 95% CI 0.30 to 1.12).	IV-A patients reported more palpitations and/or arrhythmias (OR 3.02, 95% CI 1.2 to 7.9) and vomiting (OR 4.21, 95% CI 2.2 to 8.1) with no difference in incidence of tremor (OR 2.60, 95% CI 0.6 to 11.1).
Mita et al. Intravenous aminophylline for acute severe asthma in children over two years receiving inhaled bronchodilators. Cochrane Database Syst Rev 2005;(2):CD001276. (Garfield Weston Foundation UK)	Meta-analysis of randomized controlled trials published between 1971 and 2003	To determine if the addition of intravenous aminophylline produces a beneficial effect in children with acute severe asthma who are already receiving oxygen, maximized inhaled bronchodilators and oral/intravenous glucocorticoids and to examine whether any beneficial effect of aminophylline may be influenced by the intensity of concomitant therapy	Seven trials included five from the USA, one from Australia, and one from Turkey. All were placebo controlled, double-blind randomized trials published between 1993 and 1998. Overall methodological quality was good (mean Jadad score of 4.7); all had adequate concealment of allocation.	Age Mean age between 5 and 9 yr in all studies but one in which children were slightly older Gender Not reported	Acute severe asthma Six studies conducted in emergency departments; one in an inpatient setting	Arm 1 IV-A Arm 2 Placebo (P)	Therapeutic levels considered to be 10–20 mcg/ml in 4 studies, 10.5–14.3 mcg/ml in 1 study, 12–20 mcg/ml in 1 study, and 15–20 mcg/ml in 1 study. All children were given oxygen, regular beta-agonists and glucocorticoids from the outset. In one trial, children also received nebulized ipratropium as well as beta-agonists.	*Patients receiving IV-A had greater improvement in % predicted FEV$_1$ compared to P at 6–8 hrs (8.37% pred., 95% CI 0.82 to 15.92; 2 trials), 12–18 hrs (8.15% predicted, 95% CI 1.04 to 15.27, 2 trials) and 24 hrs (8.87% predicted, 95% CI 1.24 to 16.50, 2 trials). *Patients receiving IV-A had greater improvement in PEF compared to P at 6–8 hrs (SMD 0.62, 95% CI 0.04 to 1.2), 12–18 hrs (SMD 0.75, 95% CI 0.25 to 1.26) but not at 24 hrs (SMD 0.39, 95% CI –0.51 to 1.30).	Difference in symptoms favored IV-A at 6–8 hrs (SMD –0.42, 95% CI –0.70 to –0.14; 2 trials) with no difference at 24 hrs (SMD –0.33, 95% CI –0.52 to 0.25). There was no difference in the number of nebulized bronchodilators required in 24 hrs (WMD –0.15, 95% CI –0.52 to 0.83; 2 trials). There was no difference in the length of stay (WMD –2.1 hrs, 95% CI –9.45 to 5.25, 3 trials). No data were reported on length of stay in PICU.	There was increased risk of vomiting in IV-A vs. P (RR 3.59, 95% CI 2.15 to 6.343; 5 trials) with no difference in incidence of headache, tremor, seizures, arrhythmias, hypokalaemia, and death.