Supplementary Table 1: Search terms used for databases

MEDLINE OVID search

1. exp Asthma/

2. (exac* or acute).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

3. (child* or ped* or paed*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

4. (IV or intrav* or intravenous).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

5. 1 and 2 and 3 and 4

6. controlled clinical trial.pt.

7. randomized controlled trial.pt.

8. randomized.ab.

9. placebo.ab.

10. drug therapy.fs.

11. randomly.ab.

12. trial.ab.

13. groups.ab.

14. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13

15. exp animals/ not humans.sh.

16. 14 not 15

17. 5 and 16

EMBASE OVID

1. exp asthma/

2. (exac* or acute).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]

3. (child* or ped* or paed*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]

4. (IV or intrav* or intravenous).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]

5. 1 and 2

6. 3 and 5

7. 4 and 6

8. random$.mp.

9. factorial$.mp.

10. cross over$.mp.

11. crossover$.mp.

12. cross-over$.mp.

13. placebo$.mp.

14. (doubl$ adj blind$).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]

15. (singl$ adj blind$).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading]

16. assign$.mp.
17. allocat$.mp.
18. volunteer$.mp.
19. crossover procedure/
20. double blind procedure/ 21. randomised controlled trial/ 22. single blind procedure/

23. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 24. 7 and 23

CENTRAL COCHRANE DATABASE

"asthma" in Title, Abstract, Keywords and "child' or "ped" or "paed" and "IV or intravenous" and "exac or acute" (Word variations have been searched)

International Clinical trials database

"asthma" AND "exacerbation" with selection for clinical trials in children

Table 2. Trial drugs and comparators used in studies

Trial drug	Vs. Placebo or standard care	Vs. Nebulised Magnesium	Vs. Nebulised ipratropium bromide vs. Intravenous Salbutamol plus Inhaled Ipratropium Bromide	Vs. Intravenous Salbutamol	Vs. Sub cut Adrenaline vs. Nebulised Salbutamol	Two doses vs. one dose	Bolus vs. high dose infusion	Vs. Ketamine	Vs. Terbutaline vs. Terbutaline and Aminophylline	Nebulised Salbutamol vs. Intravenous Albuterol
Aminophylline	7			3	1			1	1	
Magnesium	7	2	1	1		1	1		1	
Theophylline	4									
Doxofylline	1									
Salbutamol	2		1							1
Terbutaline	1									
Ketamine	1									
Montelukast	2									
Total	25	2	1	4	1	1	1	1	2	1

Numbers = Number of trials

Table 3. Treatment drugs and comparator dosing and regime

Trial drug	Bolus then infusion	Bolus only	Infusion only	Infusion then oral	Multiple Intravenous drugs
Magnesium		25mg/kg max 2g over 20min (1, 2) 40mg/kg max 2gm over 20min (3, 4) 50mg/kg dose over 20min (5) 50mg/kg over 20 min vs 3x 2.5ml of nebulised (6) 2x bolus vs single bolus (rate and dosing not specified)(7) 75mg/kg (Max 2.5mg) over 20min(8) .2ml/kg over 35min (9) 3x intermittant bolus (dosing and timing not specified) (10)	Infusion only – timing and dosing not specified (11)		50mg/kg over 20min vs Terbutaline 10micro/kg followed by vs IV Aminophylline 5mg/kg followed by 0.9mg/kg/hr) (12) 50mg/kg MgS04 vs 1mg/kg/min of salbutamol timing not specified(13)
Aminophylline	6mg/kg over 10min then 0.8 – 1.0 mg/kg continuous duration not specified (14) 7mg/kg -10mg/kg over one hour then 0.7 to 1.1 mg/kg clincians deciding when to cease (15) 7mg/kg bolus then	2x doses 6 hours apart of 5mg/kg(17) 5mg/kg over 10min (18) 1 vial dose and timing not specified (19)	Timing and dosage not specified (20)		4-6mg/kg (dependent on weight range) over 5min, then 0.7mg/kg -0.9mg/kg of aminophylline versus 5 micro/kg of salbutamol over 5min followed by constant infusion of 5micro/kg per hour (21) 4mg/kg bolus then 0.6mg/kg per hour for

	continuous over .75mg – 1.2 mg/kg clinicians deciding when to cease (16)				24hours of aminophylline versus salbutamol 4 micro/kg (timing not specified) then 0.6micro/kg continuously for 24 hours (22) 15micro/kg over 20min then continuous salbutamol infusion dose not specified vs aminophylline bolus of 5mg/kg over 20min then infusion of 0.9mg/kg/hr(23)
Theophylline	Bolus 1.6mg/mL (timing not defined) and continuous infusion 1.6mg/ml (24) Bolus over 30 min based on base theophylline level (to achieve target 82.5micro/L), then continuous infusion 0.8 to 1.0mg/kg per hour for 36 hours(25) Bolus of 4.8mg/kg over 20min, followed by rate of .8mg/kg per hour total timing not specified (26) Load of 7mg/kg then infusion range 0.5 – 0.65 timing unspecified (27)			Initial infusion to maintain levels at 55-110micromol/L then oral therapy plus 2 week oral at discharge (28)	IV Theophylline at 6.4mg/kg over 20min then infusion .64 - .96mg/kg versus Terbutaline 20micro/kg followed by continuous .4micro/kg/min reduced by clinical improvement(29)
Salbutamol	15micro/kg bolus over 10min (30-32)				
Terbutaline	Loading dose of 10microgram,/kg per min for 10-20 then continuous of				

Terbutaline	Loading dose of 10microgram,/kg per min for 10-20 then continuous of 1micro/kg per min duration not specified(33)				
Ketamine	.2mg/kg bolus over 1-2min then .5mg/kg per hour continunous infusion for 2 hours (34)				0.5mg/kg ketamine over 20min then infusion 0.6mg/kg/hr for 3 hour vs aminophylline 5mg/kg over 20min then 0.9mg/kg/hr(35)
Montelukast		Sinlge 10mg bolus dose (36) 5.25mg over 2-5min (37)			

Table 4: Adverse events* listed as outcome measures by trial medication

Trial drug	**Number of trials capturing adverse events as an outcome measure TOTAL**	**Specifics of adverse events if described in the paper**
Magnesium	6/13 = 45%	Dizziness, fatigue, change to body temperature (3) Hypotension, warmth, numbness, respiratory depression (9) Hypotension and vomiting (8)
Aminophylline	9/12 = 75%	Stroke volume and cardiac output, Pulses paradoxus (21) Tremor (18) Vomiting, nausea and abdominal pain (23) Arrythmia (16) Arrhythmia, Vomiting and nausea, Headache, Palpitations (15, 29)
Theophylline	4/4 = 100%	Toxicity, incsomnia, irritability, comiting, nausea, headache, seizures (24) Nausea, headache, palpitations, tremor (25) Tremor, wheezing, (26) Vomiting, nausea, abdominal pain, headache, seizures, tremor, irritability (27)
Doxofylline	1/1 = 100%	
Salbutamol	2/4 = 50%	Not specified (32) Vomiting, nausea, headache, seizures, palpitations (30)
Terbutaline	1/1 = 100%	Arrythmia(33)
Ketamine	2/2= 100%	How the child felt, Nightmares, dysphoria, behavioral change (34) Hypertension (35)
Montelukast	0/2 = 0%	

***Adverse event: defined as specific mention of a side effect eg hypotension, tremor, wheezing NOT purely listing recording of a change of observation e.g heart rate, respiratory rate, blood pressure**

Table 5: Full list of outcome measures for each study

Study/ Year	Type	Geographic location	Interventions	Number of patients and age range	Primary Outcome/s	Secondary Outcome	Other outcomes
Allen and Macias, 2005 (34)	RCT	USA	Intravenous Ketamine bolus and infusion vs placebo	66 2-18 years	Reduction of pulmonary index score of 2 points at 2 hours	Disposition of patients after completion of study	Intravenous bronchodilator utilization Need for second line therapies Rate of hospitalization Respiratory rate, Heart rate, Blood pressure, Oxygen saturation How the child felt Nightmares, dysphoria, behavioral change
Alansari, 2015 (7) Registered clinical trial *Actively recruiting*	RCT	Qatar	Intravenous Magnesium Sulphate 2x dose vs single dose	240 2 -14 years	Rate of early discharge from the pediatric emergency centre	Rate of revisits to pediatric emergency centre/primary health care Rate of change in clinical asthma score	

						Hospital length of stay Pediatric intensive care admission rate	
Bien et al/1995 (24)	RCT	USA	Intravenous Theophylline vs placebo	39 2 -10 years	Pulmonary index score every 7-9 hours for 24hours	Oxygen saturations Toxicity Aerosol requirement	Short acting beta 2 agonist requirement Oxygen saturations Occurrence of arrhythmia Vomiting, nausea, headache, seizures Toxicity, insomnia, irritability
Boeschoten /2017(32) Clinical Trial Registry Recruiting	RCT	Netherlands	Intravenous bolus salbutamol vs standard care	56 2 – 18 years	Clinical asthma score not specified	PICU length of stay, Adverse event Need for mechanical ventilation	
Bogie et al/2007 (33)	RCT	USA	Intravenous Terbutaline vs placebo	49 2-17 years	Modified CASS score mean improvement over 24hours	Length of treatment with continuous nebulized albuterol Intravenous bronchodilator utilization	Electrolytes, lactate, troponin

						Intubation Arrhythmia PICU length of stay	
Browne et al/1997(30)	RCT	Australia	Intravenous salbutamol vs placebo	29 1 – 12 years	Number of persistent moderate to severe asthma symptoms 2 hours after randomization, Time to no longer requiring inhaled salbutamol every 30min		Rate of early discharge from the pediatric emergency centre. Respiratory rate, Heart rate, Oxygen saturations, Blood pressure, vomiting, nausea, headache, seizures, palpitations, tremor, toxicity
Browne et al/ 2002 (31)	RCT	Australia	Intravenous salbutamol vs nebulized Ipratropium bromide vs Intravenous salbutamol plus inhaled ipratropium bromide	55 1-14 years	Emergency department length of stay, mean recovery time (time from randomization to no longer requiring nebulized therapy), rate of early discharge from Emergency department	Pulmonary index score > or = 7, persistent moderate to severe asthma 2 hours after randomization	
Carter et	RCT	USA	Intravenous	21	Pulmonary	Number of	Nausea,

al/1993 (25)			Theophylline vs placebo	5 – 18years	index score, Improvement in forced expiratory volume (FEV1)	salbutamol doses, Salbutamol dose (mg), hospital length of stay, adverse event	headache, palpitations, tremor
Ciarallo et al/2000 (3)	RCT	USA	Intravenous Magnesium Sulphate vs placebo	30 6 – 17.9 years	Peak expiratory flow rate (PEFR)	FEV1 Forced vital capacity (FVC) Rate of hospitalization	Asthma score (Wood-Downe) Number of salbutamol doses Number of atrovent nebulizers Spirometry BP
Ciarallo et al/1996 (1)	RCT	USA	Intravenous Magnesium Sulphate vs placebo	31 6 – 18 years	Degree of improvement in observations and FEV1, PEFR, FVC until 110min		Hospital length of stay Rates of revisit to Emergency Department/primary health care physician Respiratory rate, Heart rate, Oxygen saturations, Blood Pressure Requirements for admission to ICU, Dizziness, fatigue, change to body temperature
Cross,	RCT	USA	Intravenous	20	Hospital		

2012 (11) Clinical Trials Registry *Withdrawn*			Magnesium Sulphate vs placebo	2 – 20 years	length of stay		
Daengsuwan, 2017 (6)	RCT	Thailand	Intravenous Magnesium Sulphate vs nebulized	28 2 – 15 years	Clinical asthma score Wood Downe, Adverse event	Hospital length of stay	
D'Avila et al 2007 (17)	RCT	Brazil	Intravenous aminophylline vs placebo	60 2 – 5 years	Hospital length of stay, Disposition of patients after study, Duration of oxygen therapy	Blood pressure, Oxygen saturation, Heart rate, Respiratory rate	
Devi et al/1997 (9)	RCT	India	Intravenous Magnesium Sulphate vs placebo	47 1 – 12 years	Clinical asthma score PEFR Oxygen saturations	Readiness for discharge	Hypotension, warmth, numbness, respiratory depression Accessory muscle use, dyspnoea and color Wheezing Stroke volume and heart rate, pulses paradoxes respiratory rate, Pulse
DiGiulio et al/1993	RCT	USA	Intravenous Theophylline	29 2 – 16	Number of hospital	Nu of doses of nebulized	Heart rate, BP Tremor,

(26)			vs placebo	years	hours elapsed prior to asthma score of < or = 2	B2 Spirometry Adverse event	wheezing, accessory muscle use
Edmunds et al 1981(21)	RCT	UK	Intravenous aminophylline vs Intravenous salbutamol vs both	29 3 – 14 years	PEFR		Stroke volume and cardiac output Pulses paradoxus
Gurkan et al/1999 (4)	RCT	Turkey	Intravenous Magnesium Sulphate vs placebo	20 6 – 16 years	Clinical asthma scores at 30min PEFR		Salbutamol dose (mg) Short acting beta 2 agonist requirement Requirement for steroids Timing of nebulized therapies PICU admission rate heart rate, blood pressure, flow rate of supplemental 02, Wheezing, breath sounds, cyanosis, accessory muscle use, cerebral function
Hambleton et al/1979 (22)	RCT	UK	Intravenous Aminophylline vs Intravenous	18 1 ½ - 7 years	Clinical score not specified		Respiratory rate and heart rate

			salbutamol				
Hussein et al/1986(39)	RCT	Amsterdam	Nebulized salbutamol vs Intravenous albuterol	20 18 mth – 15 years	Clinical score not specified PEFR Respiratory rate Heart rate Blood gas		
Ibrahim et al/1993 (18)	RCT	Sudan	Intravenous aminophylline vs Subcut adrenaline vs nebulized salbutamol	120 5 – 12 years	PEFR Respiratory rate, heart rate, blood pressure		Tremor
Irazuzta et al/ 2016 (5)	RCT	Paraguay	Intravenous Magnesium Sulphate bolus vs infusion	38 6 – 16 years	Discharge home at 24hours Treatment costs	Cost implication Hospital length of stay	
Lemon, 2007 (36) Clinical trials registry *Status unknown*	RCT	USA	Intravenous Montelukast vs placebo	52 6 -18 years	Evaluate effect of intravenous of montelukast as adjuvant therapy	First dose pharmacokinetic parameters	
Morris et al/2010 (37)	RCT	USA	Intravenous Montelukast added to standard therapy vs standard therapy alone	276 6 – 14 years	Average change in FEV1 (0-60min)	Modified Pulmonary index score after 60min Number of patients requiring hospitalization or not discharged from Emergency	Average change in FEV1 in 45 min Average change in FEV1 in 2hours Rate of hospitalization Oxygen saturations

						department in 2hours	
Naao et al/ 2007 (20)	RCT	Korea	Intravenous aminophylline vs placebo	50 2 – 15 years	Change in clinical asthma severity score over time		Adverse event Wheezing
Needleman et al/1995 (28)	RCT	USA	Intravenous Aminophylline vs placebo	42 2 – 18 years	Mean length of stay Change to clinical asthma severity score	Spirometry Readiness for discharge	Oxygen saturations
Nuhoglu et al/ 1998 (14)	RCT	Turkey	Intravenous aminophylline vs placebo	38 2 – 16 years	Change in clinical asthma score over 24 hours Mean number of nebulizations of salbutamol over 24 hours	Spirometry Adverse event	
Pierson et al/ 1971 (19)	RCT	USA	Intravenous aminophylline vs placebo	23 5 – 17 years	Clinical asthma score FVC		Blood gas Need for invasive ventilation
Ream et al/2001 (27)	RCT	USA	Intravenous Theophylline vs placebo	47 13 mths – 17 years	PICU length of stay Asthma score to less 3	Hospital length of stay	Hours on continous nebulised albuterol Respiratory rate Need for invasive

							ventilation Vomiting, nausea, abdominal pain, headache, seizures, tremor, irritability
Roberts et at/2003 (23)	RCT	UK	Intravenous salbutamol vs Intravenous aminophylline	44 1 – 16 years	Asthma severity score 2 hours post treatment Hospital length of stay Duration of oxygen therapy Adverse event	Need for additional second line therapies Duration of Intravenous therapy	Oxygen saturations Intubation Vomiting and Nausea Abdominal pain
Santana et al 2001 (13)	RCT	Brazil	Intravenous Mgs04 vs salbutamol vs placebo	50 2 – upper age not listed	Respiratory rate, BP		Number of atrovent nebulisations Hospital length of stay PICU length of stay Heart rate, Oxygen saturations, duration of oxygen therapy
Scarfone et al/2000 (8)	RCT	USA	Single dose Intravenous Mg S04 vs placebo	54 1 – 18y years	Pulmonary index score improvement over 120min Determined	Rate of hospitalization Readiness for discharge	Need for albuterol Heart rate, BP Facial flushing Hypotension and vomiting

					by investigators to require hospitalization at 120 minutes		
Singhi et al/ 2014 (12)	RCT	India	Intravenous Magnesium Sulphate vs Terbutaline vs Aminophylline	100 1 -12 years	Reduction in Clinical Asthma severity score of 4 or more points	Trends in the CAS score over 12 hours Frequency of adverse events Number of hours from enrolment to resolution of wheeze, dyspnoea, retraction. Number of patients with wheeze, dyspnoea and retraction at 1 hour	Wheezing Respiratory rate, oxygen saturation
Strauss et al/1994 (16)	RCT	USA	Aminophylline bolus followed by infusion vs placebo in addition to standard care in acute asthma	31 5 – 18 years	Total length of hospital stay	Number of albuterol nebulisations in 1st 24 hours PEFR (peaked expiratory flow rates) Frequency of adverse	Wheezing, Respiratory rate and Oxygen saturation

						events Arrhythmia Vomiting, nausea, abdominal pain, headache, seizures, palpitations	
Tiwari et al 2016 (35)	RCT	India	Intravenous Ketamine vs Intravenous aminophyline	48 1 – 12 years	Change in PRAM score	Oxygen saturation Hospital length of stay Hypertension Need for invasive ventilation Change in P02 and PC02	Adverse event
Torres et al/2012 (2)	RCT	Argentina	Standard protocol vs protocol including magnesium sulphate	143 2 – 15 years	Requirement for mechanical ventilation Intubation	Asthma score Wood and Downe Hospital length of stay PICU length of stay	
Watanatham et al/2015 (10)	Pilot prospective Intravenous study	Thailand	Intravenous magnesium sulphate vs inhaled magnesium sulphate	12 2 – 8 years	Asthma severity score at 60 minutes after therapy started	Hospital length of stay	Adverse event
Wheeler et al/2005	RCT	USA	Intravenous terbutaline vs	40 3 – 15	Improvement in CAS	PICU stay Requiremen	Need for additional

(29)			Intravenous aminophylline vs Intravenous aminophylline and terbutaline	years		t for mechanical ventilation Arrhythmia	second line therapies Respiratory rate, Oxygen saturation, Blood pressure, Need for supplemental oxygen Arrhythmia, Vomiting and nausea, Headache, Palpitations Treatment costs
Yung and South/1998 (15)	RCT	Australia	Intravenous aminophylline vs placebo in addition to standard therapy in acute asthma	163 1 – 19 years	Total length of hospital stay Improvement in FEV1	Improvement in FEV1 FVC Adverse events Asthma severity score Number of salbutamol dose Dose in mg of sabutamol PICU length of stay PICU admission rate	Maximum mid-expiratory volume Area under the peak pressure time curve Irritability and tremor Headache, Seizures, Nausea, vomiting Duration of mechanical ventilation Flow rate of supplemental oxygen Duration of supplemental oxygen Respiratory rate, heart rate. Oxygen

							saturations
Zhang et al /2004 (38)	RCT	China	Intravenous doxofylline vs placebo	166 6 mth – 8 years	Wheezing at 30min		Adverse event Respiratory rate and heart rate

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