Intravenous Magnesium Sulphate in Acute Paediatric Asthma

By

Mark Riley

Word Count: 2957

I declare that this Clinical Topic Review is all my own work

Contents

Introduction

Asthma is a chronic inflammatory condition affecting the lung airways characterised by episodes of increased responsiveness to multiple stimuli[1]. In the United Kingdom 1.1 million children are affected by asthma[2], approximately 25,000 children were admitted to hospital with asthma in 2007-2008[3] with about 22 children dying from asthma per year[4,5]. The standard treatment for an acute exacerbation remains nebulised bronchodilators (β-agonists, anticholinergic drugs) and anti-inflammatory drugs (corticosteroids). Second line treatments, commenced once first line treatment has failed to make an adequate impact, include intravenous salbutamol, aminophylline (both accompanied by significant potential complications) and magnesium.

The mechanism by which magnesium has an effect in acute asthma is incompletely understood, however there is evidence that it may be through several different actions. In-vitro experiments have shown that most of the effects of magnesium are caused by a calcium antagonist action[6]. This leads to reduced acetylcholine transmission at the neuromuscular junction, reduced post-synaptic sensitivity to acetylcholine and reduced smooth muscle excitibility[7]. The combined effect is bronchial smooth muscle relaxation. It has also been shown that magnesium lowers airway inflammation by reducing mast cell histamine release[8] and neutrophil activity[9].

In adults with acute asthma, the British Thoracic Society and Scottish Intercollegiate Guideline Network Asthma Guidelines (BTS/SIGN)[10] recommend the use of intravenous magnesium in those who fail to respond to initial nebulised and corticosteroid therapy or those with life threatening asthma. The 2009 revision of the BTS/SIGN asthma guidelines state that intravenous magnesium is safe in children over 2 years of age, but that its exact place is yet to be established[10].

I have used intravenous magnesium extensively in adults with acute asthma and find it a simple and effective drug to use, but I have no experience of its use in children. The use of magnesium in children with acute asthma appears to be logical, but I felt it appropriate to assess the evidence prior to its use.

Aims

The aims of this clinical topic review are:

1. To investigate if intravenous magnesium is an effective treatment in children with acute asthma.

2. To assess the perceptions of emergency physicians regarding the role of intravenous magnesium in children with acute asthma.

Methods

Selection Criteria

For trials to be used in this review they needed to:

i. be randomised controlled trials

ii. compare intravenous magnesium sulphate with placebo

iii. Recruit children under 18 years of age with acute asthma

iv. be set in an Emergency Department (ED) or similar setting

v. use quantifiable outcome measures.

Search Strategy

Medline via Ovid Interface 1950 to March week 4 2010.

{exp Asthma OR asthma.mp} AND {exp Magnesium OR exp Magnesium Sulfate OR magnesium.mp OR MgSO4.mp} AND {exp Infusions, Intravenous OR exp Injections, Intravenous OR intravenous.mp OR iv.mp} LIMIT (humans and "all child (0 to 18 years)").

CINAHL, EMBASE, Cochrane Library, Cochrane Central Register of Controlled Trials, Pubmed and Google were all searched using the following keyword search: "magnesium" and "asthma" and "children" and "intravenous".

The references of all related studies and review articles were searched to identify any studies that had been missed with this search strategy.

Search Results

54 papers were found. 45 were excluded after reviewing the title and abstract. The full articles for the remaining nine were obtained. Of these, three were excluded; one was excluded as it was an editorial[11], one because it was a retrospective case review[12] and one because it was only available in German[13]. This left six randomised, placebo controlled trials that met the stated inclusion criteria relevant to intravenous magnesium[14-19]. One trial[19] recruited patients from the outpatient department and transferred them to a High Dependency Unit (HDU) setting for the trial. After much consideration I felt it was appropriate to include this study as the interventions described can easily be performed in an ED resuscitation room.

Critical Appraisal

The six studies included in this review are presented in a BestBets style table over the following pages. Study setting, study population, interventions used, outcome measures, key results and study weaknesses are all appraised. I have assigned a Jadad Score[20] to each of the studies.

Table Key	
PED – Paediatric Emergency Department	**ED** – Emergency Department
PEFR – Peak Expiratory Flow Rate	**%PPEFR** – Percent of Predicted PEFR
FEV1 – Forced Expiratory Flow Rate in 1s	**%PFEV1** – Percent of Predicted FEV1
PI – Pulmonary Index	**CAS** – Clinical Asthma Score
%PFVC – percent of predicted Forced Vital Capacity	**NHLBI** – National Heart, Lung and Blood Institute
PR – Pulse Rate	**RR** – Respiratory Rate
SpO2 – Oxygen Saturations	**NIBP** – Non-Invasive Blood Pressure
ABG– Arterial Blood Gas	**PICU** – Paediatric Intensive Care Unit
SPCU – Special Pediatric Care Unit	**$MgSO_4$** – Magnesium Sulphate

Table of included studies

Author, Date and Country	Population	Intervention	Co-interventions	Outcome Measures	Key Results	Study Weaknesses
Ciarallo L. USA 1996[14] *Jadad(4)*	31 children in ED of Paediatric Hospital aged 6-18 years with PEFR < 60% predicted after 3 β2 agonist nebulisers	25mg/kg IV $MgSO_4$ (maximum 2g) vs placebo in 100ml volume.	Methylprednisolone 2mg/kg. Nebulised albuterol (0.15mg/kg) as prescribed by the medical team		$MgSO_4$ vs Placebo	Underpowered No definition of asthma No description of dropouts/ withdrawals $MgSO_4$ group had significantly lower baseline FEV1. Unreliability of PEFR in children Only enrolled children over 6 years Data only obtained for 110min post-infusion. Discharge decision was actually a reversal of the decision to admit
				Change in %PPEFR	↑%PPEFR 80min 46% vs 16% (p=0.05) 110min 59% vs 20% (p=0.05)	
				Change in %PFEV1	↑%PFEV1 80min 34% vs -1% (p=0.05) 110min 75% vs 5% (p=0.05)	
				ED Discharge	Discharge – 27% vs 0% (p=0.03)	
				Adverse events	No adverse events	

Author, Date and Country	Population	Intervention	Co-interventions	Outcome Measures	Key Results	Study Weaknesses
Devi PR. India 1997[15] *Jadad (3)*	47 children in a University PED aged 1-12 years with acute severe asthma with inadequate/ poor response (defined by NHLBI guidelines)[21] after 3 salbutamol nebulisers	100mg/kg IV $MgSO_4$ vs placebo in 30ml volume.	Hydrocortisone, aminophylline and salbutamol (0.15mg/kg) nebulisers 1 – 2 hourly		$MgSO_4$ vs Placebo	No ethical approval Power calculation only performed after recruitment had stopped. Used modified PI Score (not validated) No definition of asthma. Randomisation process inadequately described Possible loss of blinding with concentrated infusions and pain etc. at infusion site Unreliability of PEFR in children
				Change in modified PI Score	Lower PI scores at 1,2,3 & 11 hours ($p<0.01$)	
				%PPEFR > 70%	at 11 hours 53% vs 12.5% ($p<0.05$)	
				Oxygen Saturation	Higher saturations at 1,2,3, & 7 hours ($p<0.05$)	
				Time to hospital discharge	13.6±6.8h vs 18.9±7.7h ($p<0.05$)	
				Adverse events	Epigastric warmth (12.5%), temporary pain (16.6%) or numbness/tingling (12.5%) at the infusion site.	
Gurkan F. Turkey 1999[16] *Jadad (2)*	20 children in a University PED aged 6-16 years with a PEFR < 60% predicted after 3 salbutamol nebulisers	40mg/kg IV $MgSO_4$ (maximum 2g) vs placebo in 100ml volume.	Methylprednisolone 2mg/kg Nebulised salbutamol (0.15mg/kg) with no description of frequency	Change in %PPEFR	$MgSO_4$ vs placebo 30min 43±6.3% vs 14.6±3.7% ($p=0.0002$) 90min 58.4±2.9% vs 21.8±4.5% ($p=0.0001$)	No ethical approval No power calculation, and used a small convenience sample No description of randomisation, blinding or dropouts No description of asthma Unreliability of PEFR in children Only enrolled children over 6 years Data only collected for 90min post infusion
				Change in CAS[22] from baseline	30min $MgSO_4$ 4±0.5 vs 5.8±0.4($p=0.005$) Placebo 5.5±0.5 vs 5.7±0.5($p>0.005$) 90min $MgSO_4$ 2.5±0.5 vs 5.8±0.4($p=0.005$)	
				Adverse events	No adverse events	

Author, Date and Country	Population	Intervention	Co-interventions	Outcome Measures	Key Results	Study Weaknesses
Scarfone RJ. USA 2000[17] *Jadad (5)*	54 children in an ED of a Paediatric Hospital aged 1-18 years with moderate to severe asthma as determined by using PI Score[23]	75mg/kg IV $MgSO_4$ (maximum 2.5g) vs placebo. No description of volumes.	Methylprednisolone 1mg/kg. Nebulised albuterol (0.15mg/kg) at 0, 40, 80 and 120 minutes		$MgSO_4$ vs placebo	Inadequate description of randomisation process Underpowered Change in age limits for recruitment for the last 5 months No description of length of study or infusion volumes Children enrolled despite response to first nebuliser Data only collected for 150min in total
				Difference in PI Score	No significant difference in PI Score at any time point.	
				Difference in admission rate	-7% (95% CI -19% to 34%)	
				Time to meet discharge criteria	101min vs 96 min (p=0.75)	
				Adverse events	1 child in placebo group developed vomiting	
Ciarallo L. USA 2000[18] *Jadad (4)*	30 children in an ED of a Paediatric Hospital aged 6 to 17.9 years in EDs of 2 Paediatric Hospitals with PEFR <70% predicted after 3 bronchodilator nebulisers	40mg/kg IV $MgSO_4$ (max 2g) vs placebo in 100ml volume.	Methylprednisolone 2mg/kg Nebulised bronchodilators as prescribed by the medical team		$MgSO_4$ vs placebo	Underpowered 8 children not recruited because of "inadequate spirometry effort" Inadequate description of randomisation method. Adverse events not reported No definition of asthma Unreliability of PEFR in children Only recruited children older than 6 years Previous publication
				Change in %PPEFR, %PFEV, %PFVC	All Improved from 20min to 110min (p<0.001)	
				Difference in CAS	95min 1.4 vs 2.5 (p<0.001) 110min 1.1 vs 2.4 (p<0.001)	
				ED Discharge	50% vs 0% (p=0.02)	

Author, Date and Country	Population	Intervention	Co-interventions	Outcome Measures	Key Results	Study Weaknesses
Santana JC. Brazil 2001[19] *Jadad (3)*	50 children in outpatients admitted directly to an High Dependency Unit setting, aged 2-13 years with severe asthma refractory to salbutamol nebulisers	50mg/kg IV $MgSO_4$ vs 20mg/kg IV salbutamol vs placebo in 0.3ml/kg volume.	Intravenous hydration, oxygen, hydrocortisone (5mg/kg) and nebulised salbutamol (0.15mg/kg)		$MgSO_4$ vs salbutamol vs placebo	Not ED based No power calculation. Convenience sample used Evidence of data trawling. 12 patients lost for " various reasons" Inadequate description of randomisation process Treating nurse not blinded Use of surrogate end points Previous PICU, SPCU & "nursery" admissions higher in $MgSO_4$ group No definition of asthma or severity.
				PR, RR, SpO2, NIBP	$MgSO_4$ – transiently lower NIBP during infusion (p=0.003) Salbutamol – lower RR during (p=0.05) and 1 hour after infusion (p=0.02)	
				ABGs	Both $MgSO_4$ and placebo improved pH (p<0.001) and pCO2 (p=0.004) at 1 hour	
				Total number of nebulisers	$MgSO_4$ – no effect salbutamol – reduced (p=0.009)	
				Number of nebulisers per day	$MgSO_4$ – no effect salbutamol – reduced (p<0.001)	
				Number of days on oxygen	$MgSO_4$ – no effect salbutamol – reduced (p=0.04)	
				Number of days in hospital, PICU & SPCU	No effect in any group	
				Adverse events	Tachycardia (3 vs 5 vs 0) Flushing (2 vs 0 vs 0) Shaking (1 vs 0 vs 0) Hypocalcaemia (0 vs 1 vs 0)	

The main findings from these studies are:

Changes in Peak Expiratory Flow Rate (PEFR)

Four of the studies looked at changes in the percentage of the predicted peak expiratory flow rate (%PPEFR) as an outcome measure[14-16,18]. All four found a statistically significant improvement at various time points.

Changes in Forced Expiratory Volume in 1s (FEV1)

Only the two Ciarallo trials[14,18] used change in percentage of the predicted FEV1 (%PFEV1) as an outcome measure and both demonstrated statistically significant improvements with magnesium.

Discharge

Both Ciarallo studies[14,18] looked at ED discharge rates and found significant increases with intravenous magnesium. They found a discharge rate of 27% with 25mg/kg of intravenous magnesium sulphate versus 0% with placebo (p=0.03), giving a Number Needed to Treat (NNT) of four to prevent one admission[14]. In 2000, they demonstrated that 40mg/kg of intravenous magnesium improved ED discharge rate from 0% with placebo to 50%, giving a NNT of 2 to prevent 1 admission[18]. Devi[15] looked at time to hospital discharge and found a statistically significant reduction with intravenous magnesium.

Scarfone[17] looked at both admission rate and time to hospital discharge in children given 75mg/kg magnesium sulphate presenting with moderate to severe asthma irrespective of their response to nebulised therapy. They found no statistical difference in either of these outcome measures in this study population. Santana[19] looked at time in hospital as one of many secondary outcome measures and did not find any statistical difference between intravenous salbutamol, magnesium or placebo.

Asthma Severity Scores

Two studies[16,18] used Clinical Asthma Score (CAS)[22] as an outcome measure and found statistically significant improvements with magnesium. Devi[15] demonstrated a statistically significant improvement in modified Pulmonary Index (PI) Score with magnesium, while Scarfone[17] used an unmodified PI Score[23] as their primary outcome measure and found no difference in their study population.

Oxygen Saturations

Only 2 studies looked at oxygen saturation as an outcome measure[15,19]. Santana[19] found that there was no difference in oxygen saturations between the salbutamol, magnesium and placebo groups, however Devi[15] demonstrated a statistically significant improvement in oxygen saturation level with magnesium from 1 hour post infusion.

Other outcomes

Santana[19] used several other outcome measures, including basic observations, arterial blood gas variables, number of days on oxygen, number of nebulisers per day, total number of nebulisers, number of days on Paediatric Intensive Care (PICU), number of days on Special Paediatric Care Unit (SPCU) and number of days in hospital. The only parameters that improved with magnesium compared to placebo were arterial pH and carbon dioxide tension (pCO2), whereas intravenous salbutamol transiently reduced respiratory rate, improved the same blood gas variables, reduced the number of days on oxygen, reduced the number of nebulisers per day and the total number of nebulisers needed.

Adverse Events

Only five of the studies stated that adverse events were recorded[14-17,19]. Three of these reported that there were no adverse events[14,16,17] and only minor adverse events were reported in the other two[15,19]. The overall rate of adverse events was 8%.

Study Weaknesses

The included studies have Jadad Scores[20] ranging from two to four (out of a possible five), none are ideal and all have significant weaknesses which are detailed in the table.

In summary, none of the trials include a CONSORT diagram, but four[15,17-19] attempt to describe those patients that were lost from the trial.

Gurkan[16] and Santana[19] only used convenience samples and did not perform power calculations, while both Ciarallo studies[14,18] and the Scarfone study[17] were underpowered.

Only four studies demonstrated ethical approval[14,17-19] while only the 1996 Ciarallo study[14] provides an adequate description of the randomisation process. Even though Gurkan[16] is the only study not to provide an adequate description of their blinding methods there is evidence of potential loss of blinding in the Devi[15] and Santana[19] studies.

Santana[19] used seventeen different outcome measures with only two surrogate end points (arterial blood gas values) demonstrating a statistical significance in the magnesium group. This is suggestive of data trawling and, with the use of a small convenience sample, both type one (false positive) and type two (false negative) errors are highly likely.

Finally, it is impossible to ascertain how much children suffering from bronchiolitis contaminated the study population in the Scarfone trial[17] and with already being slightly underpowered, there is a risk that this study may have provided a false negative result.

Personal Work

I wanted to assess how Emergency Medicine (EM) colleagues perceive the role of magnesium in paediatric asthma. A pilot questionnaire was sent to all consultants and middle grade doctors working in one ED. The questionnaire was then modified to address the issues highlighted in the pilot and two separate questionnaires were then rolled out. The first was sent to the clinical or paediatric lead of every ED in the North West Deanery regarding departmental protocols (appendix 3). The second questionnaire was sent to all North West EM and Paediatric Emergency Medicine (PEM) trainees and consultants regarding their personal practice and perceptions (appendix 4).

Two follow up reminder emails were sent to each cohort in an attempt to achieve a reasonable response rate.

Despite this, the response rate for the survey regarding departmental protocols was 47% (8/17). It found that 75% (6/8) of responding EDs had a protocol, of which only 33% (2/6) included magnesium sulphate as a treatment option for children. These both stated it was to be considered in severe exacerbations, one after intravenous salbutamol and the other simply stated that they followed BTS guidelines.

The response rate was only 57.7% (71/123) for the second questionnaire. It found that only 43.7% of respondents had used magnesium in children before, but 100% would use it in the future, with most people (79%) using it in asthmatics with a severe exacerbation after failure to respond to three nebulised bronchodilators (55.2%). Full analyses of the surveys are included in appendices 5 and 6.

Discussion

Presently, magnesium sulphate is not part of many departmental protocols for paediatric asthma, despite its presence in the BTS/SIGN guidelines[10]. Despite this most EM trainees and consultants would consider using it in the future. The evidence from this review appears to support this consideration.

All six of the studies included in this topic review used different inclusion/exclusion criteria, treatments and outcome measures, making them heterogeneous. It is therefore difficult to combine the data.

However, four studies[14-16,18] suggest that intravenous magnesium is beneficial in children with moderate to severe asthma resistant to three nebulised bronchodilators. Just as importantly it appears to be a safe drug with no serious adverse events reported and a combined incidence of 8% for minor side effects. It is important to remember, however, that with only 202 children included in the trials that did report on adverse events there may still be insufficient power to detect possible rare complications.

All the children in these four studies[14-16,18] also received corticosteroids and regular nebulisers. This is consistent with what is considered appropriate first line therapy.

These four studies[14-16,18] used a PEFR of 60-70% predicted or the NHLBI guidelines[21] definition of severe asthma (which includes PEFR of less than70% predicted amongst other markers) as their inclusion criteria. These values are similar to those used in the UK and the findings are therefore transferable to moderate and severe asthma in the UK setting.

Three of the four trials that demonstrate a beneficial effect only recruited children older than six years because of the need to perform PEFRs[14,16,18]. Devi[15] enrolled younger children by using the other parameters from the NHLBI guidelines[21], however the mean age in this study was 6.7 years

with wide confidence intervals and no subgroup analysis for age. Caution should therefore be applied if extrapolating this data to younger children. It should also be noted that although the BTS/SIGN guidelines[10] recommend the use of PEFR to assess asthma severity in children older than 5 years it has been suggested that PEFR may be unreliable in the acute settings[14]. Four trials[15-18] tried to address this issue by using asthma severity scores, however these inevitably introduce an element of subjectivity to the assessment.

The outcome measures used in the 4 trials that demonstrated a benefit included changes in pulmonary function[14-16,18] , changes in illness severity scores[14,16,18], disposition from ED[14,18], and time to hospital discharge[15]. Changes in pulmonary function and severity scores are used because they have been shown to be reliable (in the correct population) and easily reproducible. There is debate about how meaningful these are to the patient though. They do not assess the patients' feelings of breathlessness or well being. ED disposition or time to hospital discharge may be a more meaningful outcome measure.

Ciarallo reported a Number Needed to Treat (NNT) of four with 25mg/kg magnesium[14] and a NNT of two with 40mg/kg[18] to prevent one admission. All the trials that discharged children from the ED also followed them up by telephone 24 – 72 hours later and no one had required further medical attention[14,17,18]. Only Devi[15] recorded data beyond a few hours and showed a reduction in length of hospital stay from 18.9±7.7h to 13.6±6.8h ($p<0.05$).

As the BTS/SIGN guidelines[10] state that a child should only be discharged once stable on 4 hourly inhaled salbutamol, a child who has required intravenous magnesium would not be discharged directly from the ED in the UK due to the emergency care 4 hour target. However these findings suggest that children who received intravenous magnesium may have an earlier hospital discharge.

Scarfone[17] showed that providing intravenous magnesium to all children with moderate to severe asthma irrespective of their response to initial nebulisers did not improve PI Score, time to discharge or ED disposition. Santana[19] found intravenous magnesium had no significant effect on any of their outcome measures that are meaningful, but did demonstrate an effect with salbutamol. This paper did have some quite fundamental flaws in its methodology that make interpreting its results difficult.

My search strategy also highlighted three meta-analyses[24-26] and one systematic review[27] related to the subject. The systematic review[27] and the Alter[24] meta-analysis were from 2000 and only included the 1996 Ciarallo[14] and Devi[15] trials. Alter[24] did not analyse the data from the paediatric population separately from the adults, therefore is difficult to apply its findings of "a statistically significant beneficial effect" directly to children. Rowe et al[27] performed sub-group analyses and concluded that there was a beneficial effect of magnesium on lung function and admission rates in children with severe asthma. Cheuk[25] looked solely at intravenous magnesium in paediatric asthma in 2005 and used five of the six trials used in this review[14-18]. They found a beneficial effect on admissions, lung function and asthma severity scores in children with moderate to severe asthma. Mohammed[26] performed a meta-analysis on intravenous and nebulised magnesium in adults and children. They used the same five trials[14-18] as Cheuk[25] in their analysis of intravenous magnesium in children and also found a significant beneficial effect on respiratory function and admission rates.

In this review I have used the same 5 trials as those assessed in the published meta-analyses, and have also included one further trial[19]. My conclusions concur with the published analyses.

Of interest, there have been two trials on nebulised magnesium in paediatric asthma and both were included in the meta-analysis by Mohammed[26]. Meral[28] compared nebulised magnesium to nebulised salbutamol in acute asthma and found that salbutamol was more effective. Mahajan[29]

compared nebulised albuterol and magnesium to nebulised albuterol and placebo in children with a mild to moderate asthma attack and found an improvement in pulmonary function at 10 and 20 minutes in the magnesium group compared to placebo. Admission rates were unaffected. Although not conclusive this has highlighted the potential benefits of nebulised magnesium in children and there is now an ongoing large UK based multicentre prospective randomised double-blinded placebo-controlled trial to look at the role of nebulised magnesium in children with acute severe asthma[30]. The trial is expected to conclude in November 2010.

Conclusion

Intravenous magnesium appears to be safe in children and of some benefit in children over five years old with moderate or severe asthma that is resistant to standard nebulised therapy and corticosteroids. Further high quality studies are needed to answer this question definitively. Other possible areas of research include dose-response studies, trials in children younger than five years and trials comparing intravenous magnesium, salbutamol and aminophylline in an attempt to rationalise the hierarchy of intravenous therapies to be used in paediatric asthma.

Further Personal Work

As a result of this topic review, I redesigned the paediatric asthma protocol in the ED in which I was employed at the time of writing to include magnesium. This incorporated a review of the paediatric departmental protocol and the evidence regarding intravenous salbutamol and aminophylline[10, 31-46] (appendix 7). I presented the new protocol, with the evidence from this topic review, to the consultant body in the weekly consultant meeting and the protocol has now been introduced. The use of the protocol will be audited 6 months after its introduction into clinical practice in the ED.

Appendix 1. Pulmonary Index Score[23]

Score	Respiratory Rate (breaths/minute)	Wheezing	Inspiration: Expiration Ratio	Accessory Muscle Use	Oxygen Saturation (%)
0	≤ 30	None	2:1	None	99 – 100
1	31 – 45	End expiration	1:1	+	96 – 98
2	46 – 60	Entire expiration	1:2	++	93 – 95
3	>60	Inspiration and Expiration without stethoscope OR silent chest	1:3	+++	<93

For children older than 6 years of age use a different respiratory rate range:

≤ 20 = 0, 21 – 35 = 1, 36 – 50 = 2, >50 = 3

The modified PI Score used by Devi[16] did not use I:E ratio.

Appendix 2. Clinical Asthma Score (CAS)[22]

Score	pO2 (mmHg) or cyanosis	Inspiratory breath sounds	Accessory muscle use	Expiratory wheezing	Cerebral Function
0	70 – 100 in air No cyanosis	Normal	None	None	Normal
1	≤ 70 in air Cyanosis in air	Unequal	Moderate	Moderate	Depressed or Agitated
2	≤70 in 40% oxygen Cyanosis in 40% O2	Decreased or absent	Maximal	Marked	Coma

pO2, arterial oxygen tension mmHg, millimetres of mercury

Appendix 3. Departmental Protocol Survey

1. Does the department in which you are currently employed have a protocol for the management of acute paediatric asthma?

- ○ Yes
- ○ No

2. Does the departmental protocol for paediatric asthma include the use of IV magnesium?

- ○ Yes
- ○ No

3. At what severity does the paediatric asthma protocol first suggest the use of IV magnesium?

- ○ Mild
- ○ Moderate
- ○ Severe
- ○ Life Threatening

4. At which point in the treatment algorithm does the paediatric asthma protocol suggest the first use of IV magnesium?

- ○ At Presentation
- ○ After failure to respond to 3 bronchodilator nebulisers
- ○ After IV salbutamol
- ○ After IV aminophylline
- ○ After both IV salbutamol and aminophylline
- ○ Pre-intubation
- ○ Only after discussion with PICU
- ○ Other (please specify)

[ ]

Appendix 4. Personal Experience Survey

1. Which best describes your training?

- ○ Emergency Medicine
- ○ Paediatric Emergency Medicine

2. Which grade are you currently employed as?

- ○ Consultant
- ○ SpR/StR

3. Have you ever used IV magnesium in acute paediatric asthma?

- ○ Yes
- ○ No

4. What degree of severity of acute paediatric asthma have you used IV magnesium for in the past?
(You may tick more than one box if you have used IV magnesium in paediatric asthma more than once before)

- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Life Threatening

5. At which point in the treatment strategy of acute paediatric asthma have you used IV magnesium in the past?
(You may tick more than one box if you have used IV magnesium in paediatric asthma more than once before)

- ☐ At presentation
- ☐ After failure to respond to 3 bronchodilator nebulisers
- ☐ After IV salbutamol
- ☐ After IV aminophylline
- ☐ After both IV salbutamol and aminophylline
- ☐ Pre-intubation
- ☐ Only after discussion with PICU
- ☐ Other (please specify)

6. What dose of IV magnesium for acute paediatric asthma have you used in the past? (You may tick more than one box if you have used IV magnesium in paediatric asthma more than once before)

- ☐ 25mg/kg
- ☐ 40mg/kg
- ☐ 50mg/kg
- ☐ 75mg/kg
- ☐ 100mg/kg
- ☐ I can't remember
- ☐ Other (please specify)

7. Has there been any adverse events noted with IV magnesium in paediatric asthma?

- ☐ None
- ☐ Tingling/Pain
- ☐ Flushing
- ☐ Epigastric warmth
- ☐ Hypotonia
- ☐ Hypotension
- ☐ Arrhythmia
- ☐ Other (please specify)

8. Would you consider using IV magnesium in acute paediatric asthma in the future?

- ○ Yes
- ○ No

9. At what severity of asthma would you start to consider using IV magnesium in children?

- ○ Mild
- ○ Moderate
- ○ Severe
- ○ Life Threatening

10. At which point in the treatment strategy of acute paediatric asthma would you first consider using IV magnesium?

- ○ At presentation
- ○ After failure to respond to 3 bronchodilator nebulisers
- ○ After IV salbutamol
- ○ After IV aminophylline
- ○ After both IV salbutamol and aminophylline
- ○ Pre-intubation
- ○ Only after discussion with PICU
- ○ Other (please specify)

11. What dose of IV magnesium are you likely to use?

- ○ 25mg/kg
- ○ 40mg/kg
- ○ 50mg/kg
- ○ 75mg/kg
- ○ 100mg/kg
- ○ I don't know
- ○ Other (please specify)

12. Are there any reasons why you would not use IV magnesium in the future?
(You may tick more than one box)

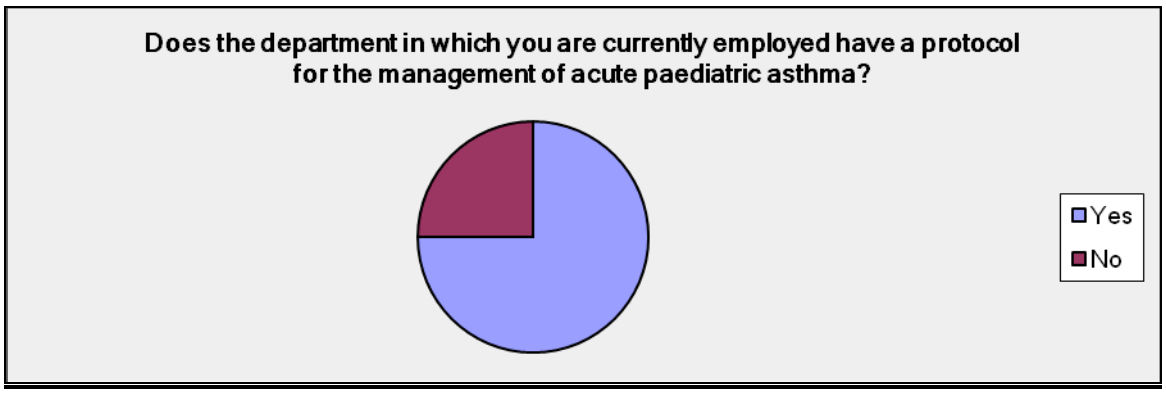
- ☐ No evidence that it is of benefit
- ☐ There is evidence of harm
- ☐ It is not recommended by BTS/SIGN guidelines
- ☐ Other drugs work better
- ☐ I can't give a reason
- ☐ Other (please specify)

Appendix 5. Results from Departmental Protocol Survey

Departmental Protocols for Acute Paediatric Asthma

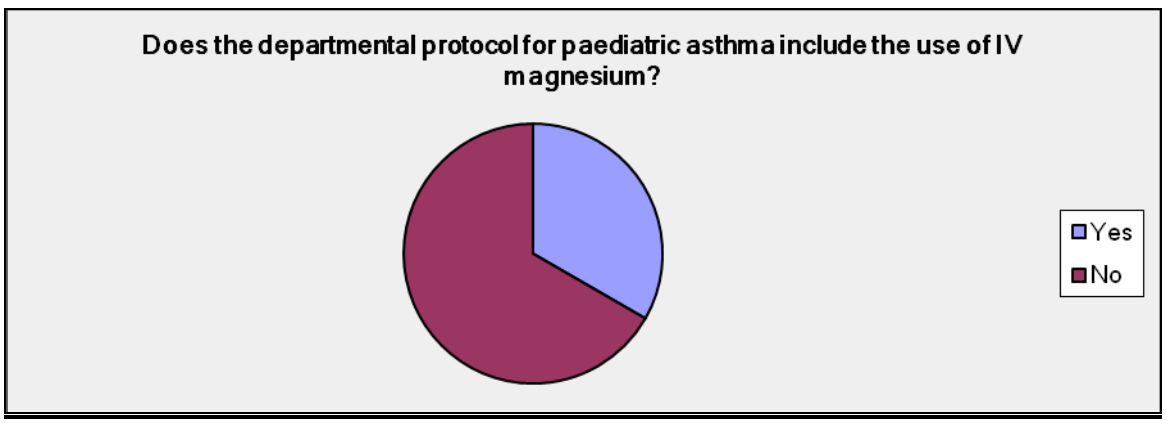
1.Does the department in which you are currently employed have a protocol for the management of acute paediatric asthma?

Answer Options	Response Percent	Response Count
Yes	75.0%	6
No	25.0%	2
answered question		8
skipped question		0

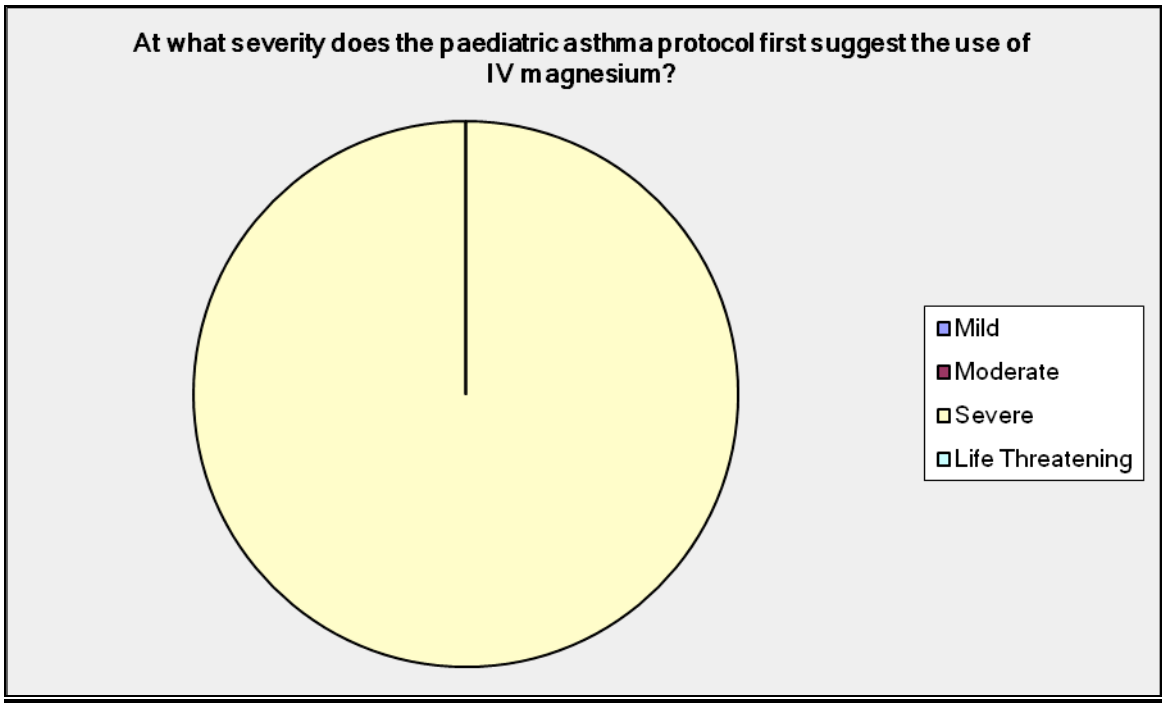


2.Does the departmental protocol for paediatric asthma include the use of IV magnesium?

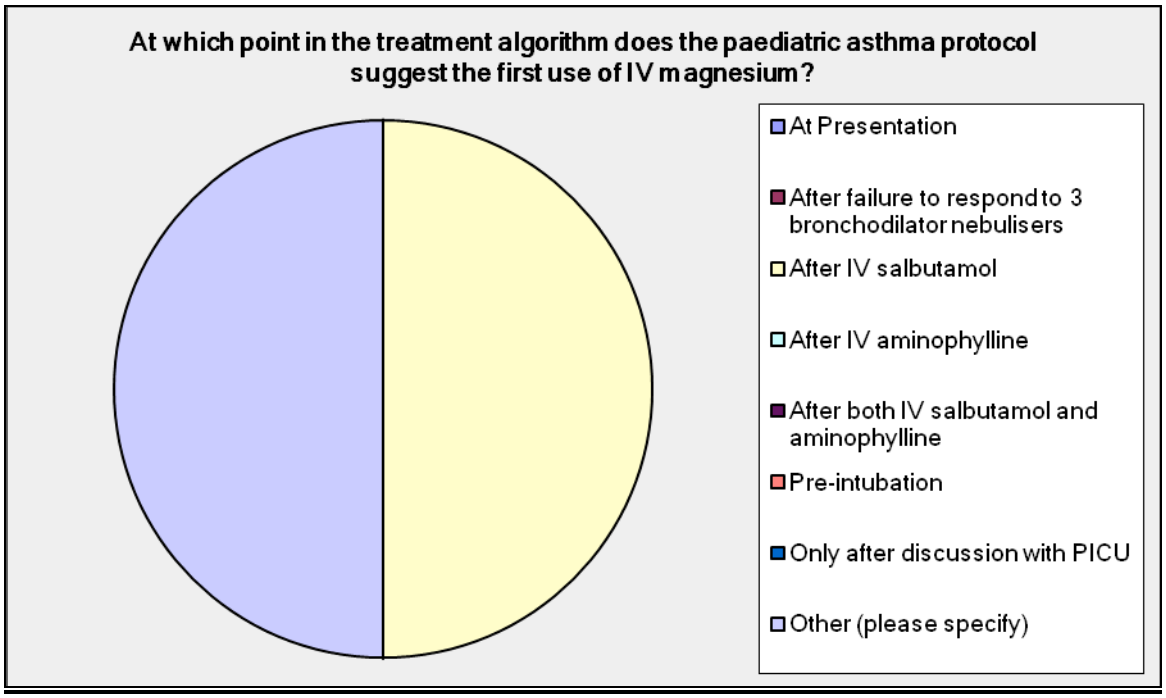
Answer Options	Response Percent	Response Count
Yes	33.3%	2
No	66.7%	4
answered question		6
skipped question		2



3.At what severity does the paediatric asthma protocol first suggest the use of IV magnesium?		
Answer Options	**Response Percent**	**Response Count**
Mild	0.0%	0
Moderate	0.0%	0
Severe	100.0%	2
Life Threatening	0.0%	0
answered question		2
skipped question		6



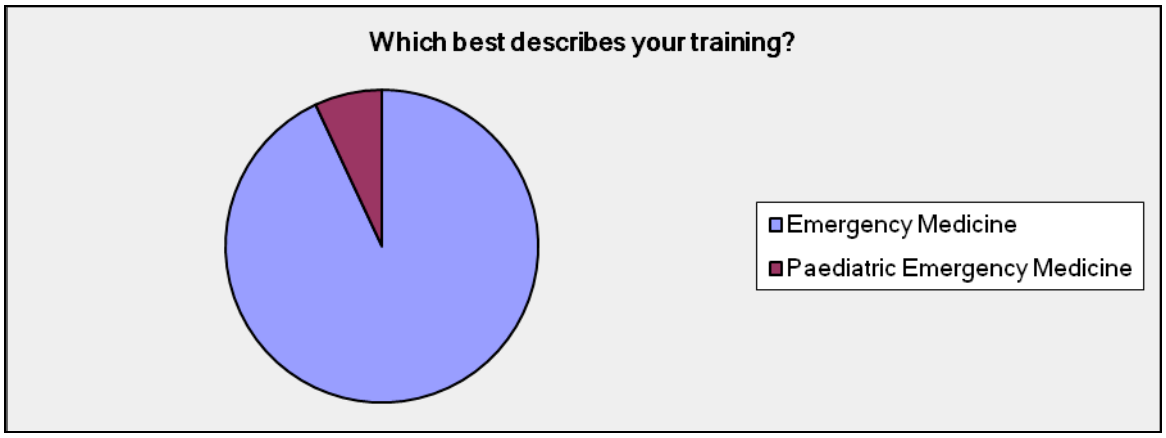
4.At which point in the treatment algorithm does the paediatric asthma protocol suggest the first use of IV magnesium?		
Answer Options	**Response Percent**	**Response Count**
At Presentation	0.0%	0
After failure to respond to 3 bronchodilator nebulisers	0.0%	0
After IV salbutamol	50.0%	1
After IV aminophylline	0.0%	0
After both IV salbutamol and aminophylline	0.0%	0
Pre-intubation	0.0%	0
Only after discussion with PICU	0.0%	0
Other (please specify)	50.0%	1
answered question		2
skipped question		6



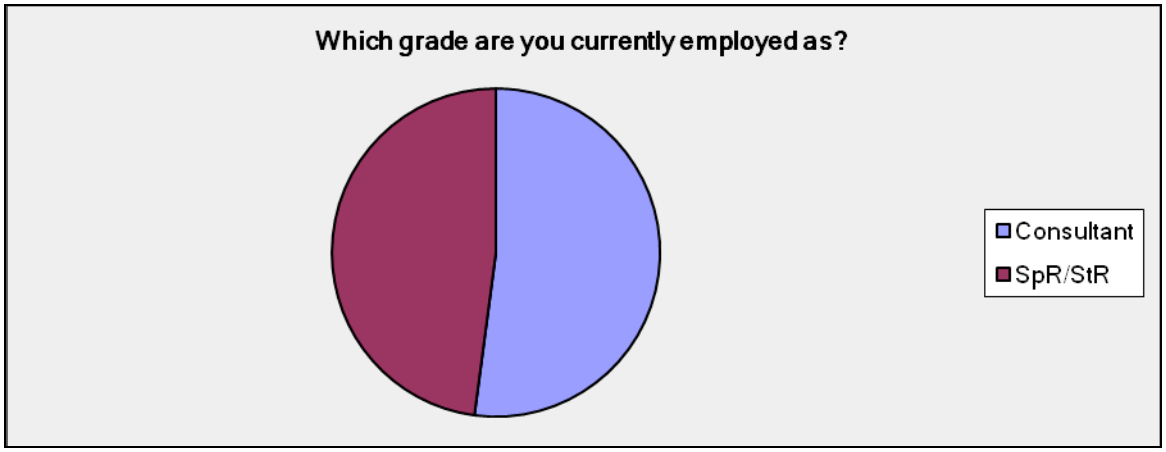
Appendix 6. Results of Personal Experience Survey

Intravenous Magnesium in Acute Paediatric Asthma

1.Which best describes your training?		
Answer Options	**Response Percent**	**Response Count**
Emergency Medicine	93.0%	66
Paediatric Emergency Medicine	7.0%	5
answered question		71
skipped question		0

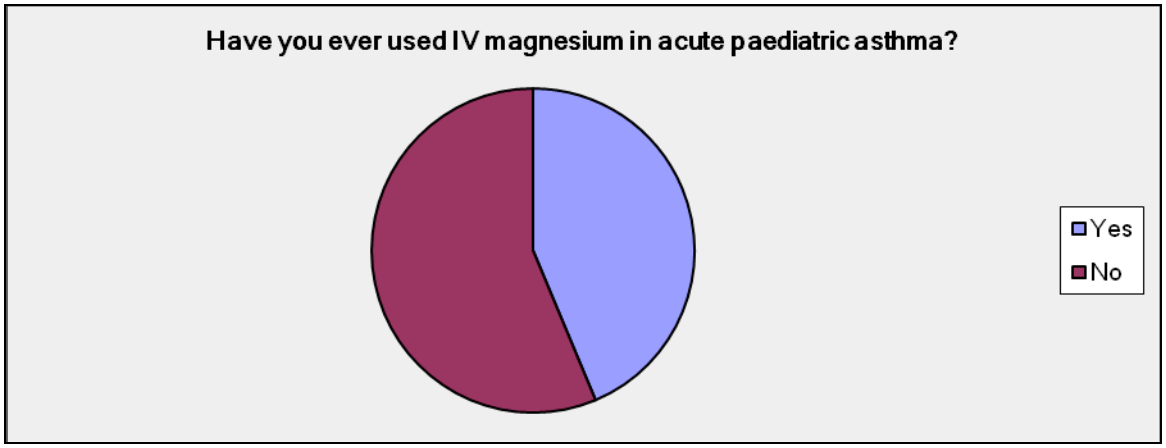


2.Which grade are you currently employed as?		
Answer Options	**Response Percent**	**Response Count**
Consultant	52.1%	37
SpR/StR	47.9%	34
answered question		71
skipped question		0



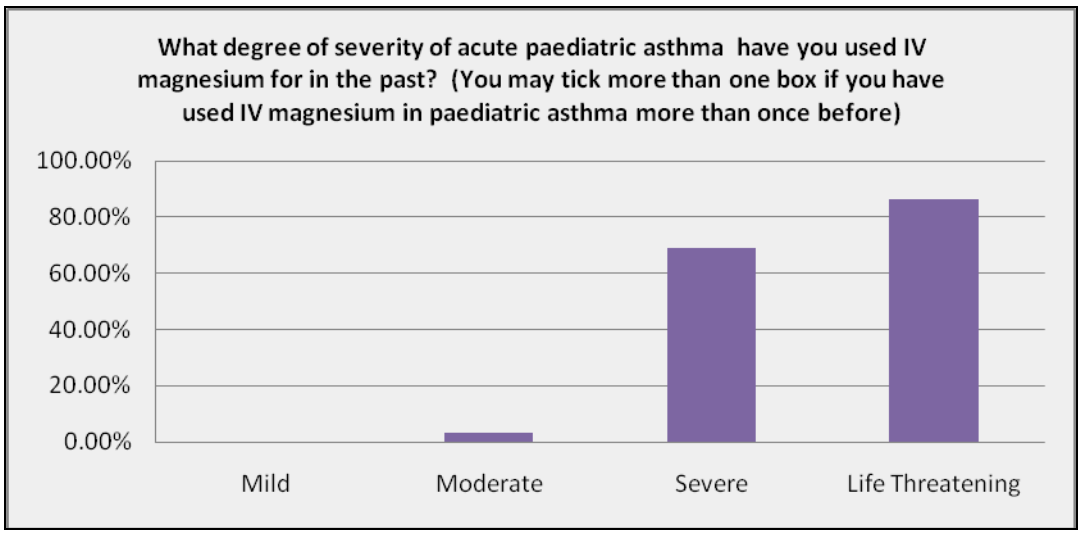
3.Have you ever used IV magnesium in acute paediatric asthma?

Answer Options	Response Percent	Response Count
Yes	43.7%	31
No	56.3%	40
answered question		71
skipped question		0



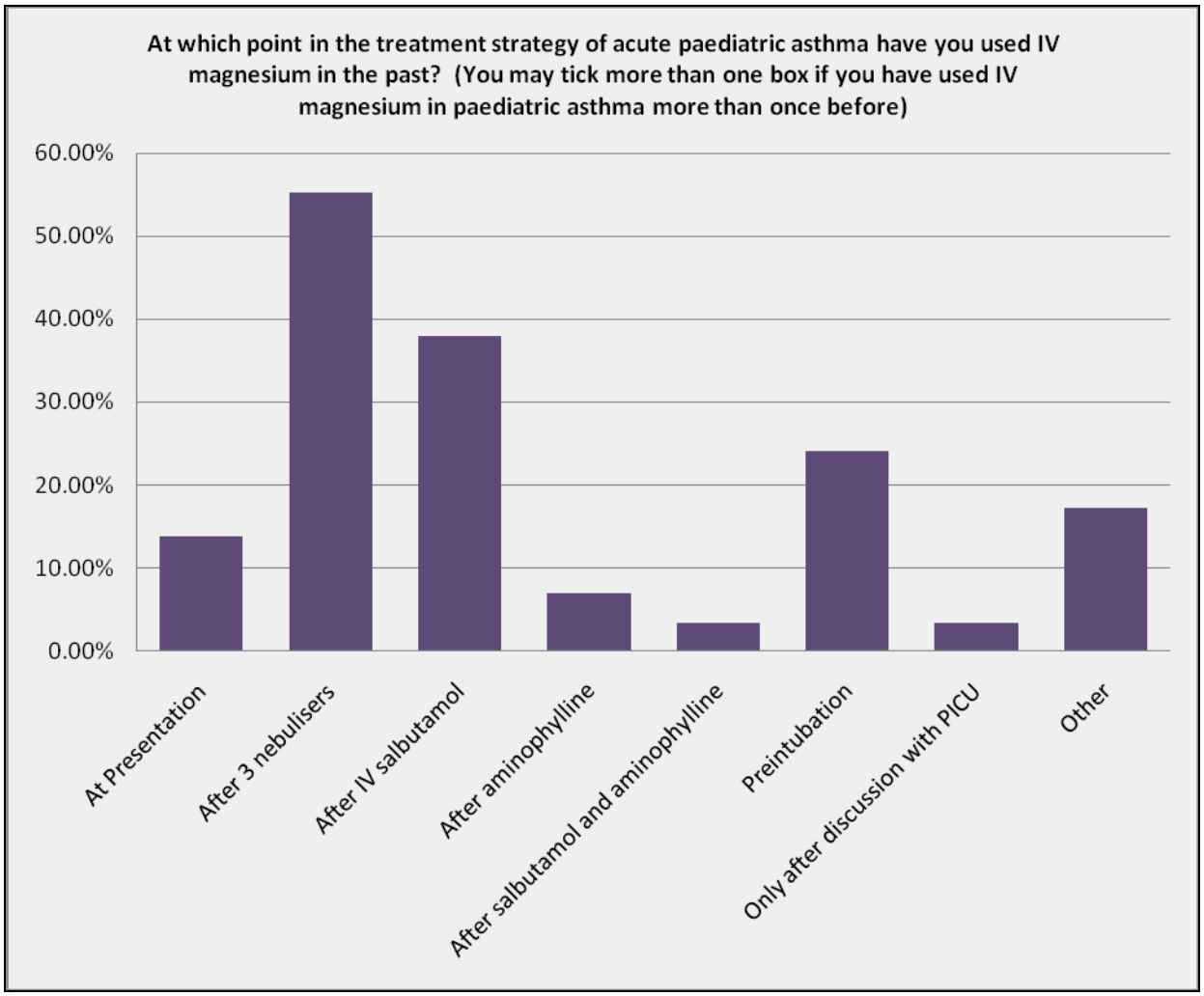
4.What degree of severity of acute paediatric asthma have you used IV magnesium for in the past? (You may tick more than one box if you have used IV magnesium in paediatric asthma more than once before)

Answer Options	Response Percent	Response Count
Mild	0.0%	0
Moderate	3.4%	1
Severe	69.0%	20
Life Threatening	86.2%	25
answered question		29
skipped question		42



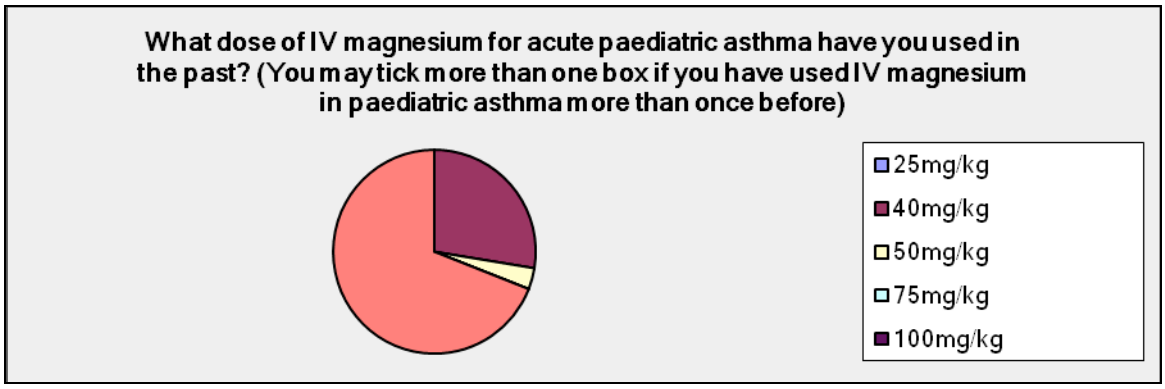
5.At which point in the treatment strategy of acute paediatric asthma have you used IV magnesium in the past? (You may tick more than one box if you have used IV magnesium in paediatric asthma more than once before)

Answer Options	Response Percent	Response Count
At presentation	13.8%	4
After failure to respond to 3 bronchodilator nebulisers	55.2%	16
After IV salbutamol	37.9%	11
After IV aminophylline	6.9%	2
After both IV salbutamol and aminophylline	3.4%	1
Pre-intubation	24.1%	7
Only after discussion with PICU	3.4%	1
Other (please specify)	17.2%	5
answered question		29
skipped question		42



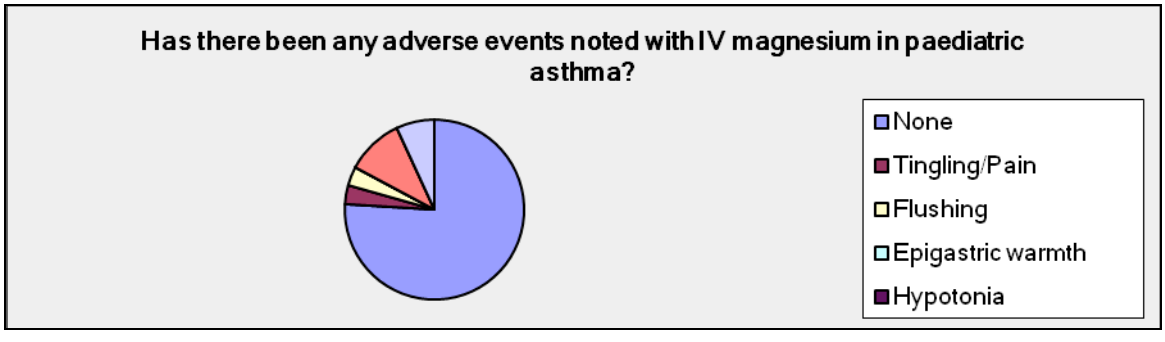
6.What dose of IV magnesium for acute paediatric asthma have you used in the past? (You may tick more than one box if you have used IV magnesium in paediatric asthma more than once before)

Answer Options	Response Percent	Response Count
25mg/kg	0.0%	0
40mg/kg	27.6%	8
50mg/kg	3.4%	1
75mg/kg	0.0%	0
100mg/kg	0.0%	0
I can't remember	69.0%	20
Other (please specify)	0.0%	0
answered question		29
skipped question		42

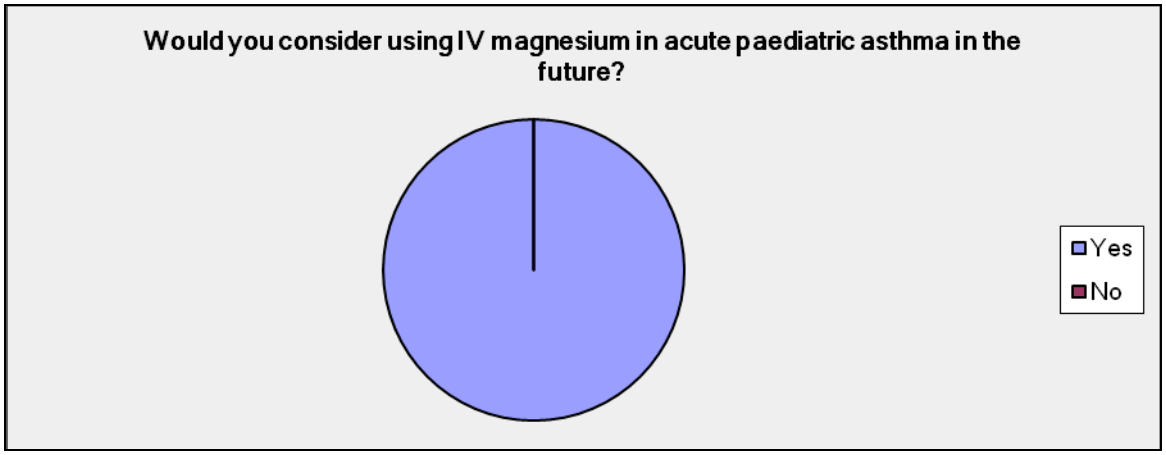


7. Has there been any adverse events noted with IV magnesium in paediatric asthma?

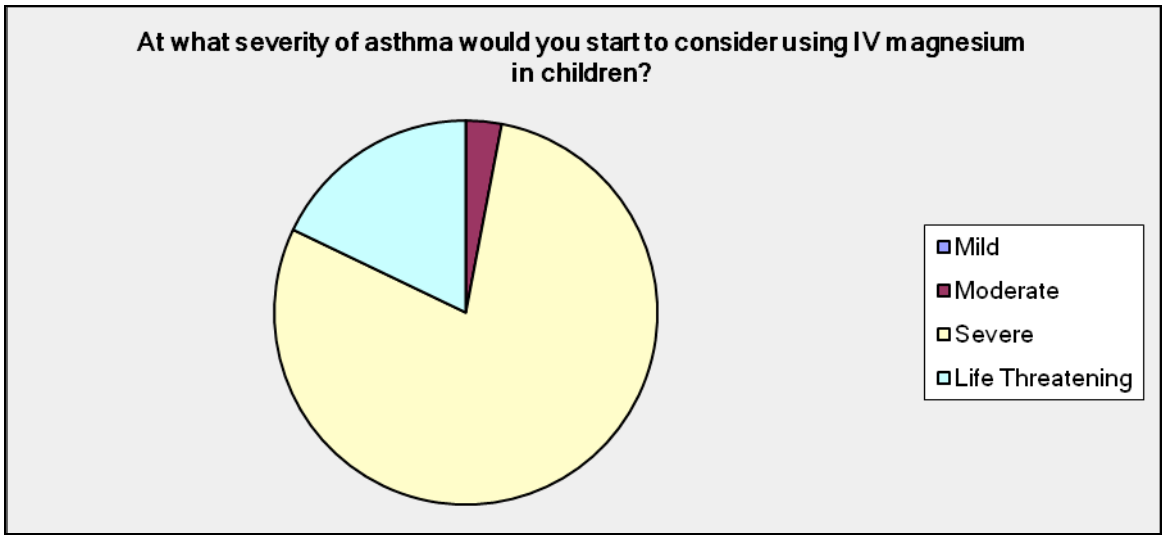
Answer Options	Response Percent	Response Count
None	75.9%	22
Tingling/Pain	3.4%	1
Flushing	3.4%	1
Epigastric warmth	0.0%	0
Hypotonia	0.0%	0
Hypotension	10.3%	3
Arrhythmia	0.0%	0
Other (please specify)	6.9%	2
answered question		29
skipped question		42



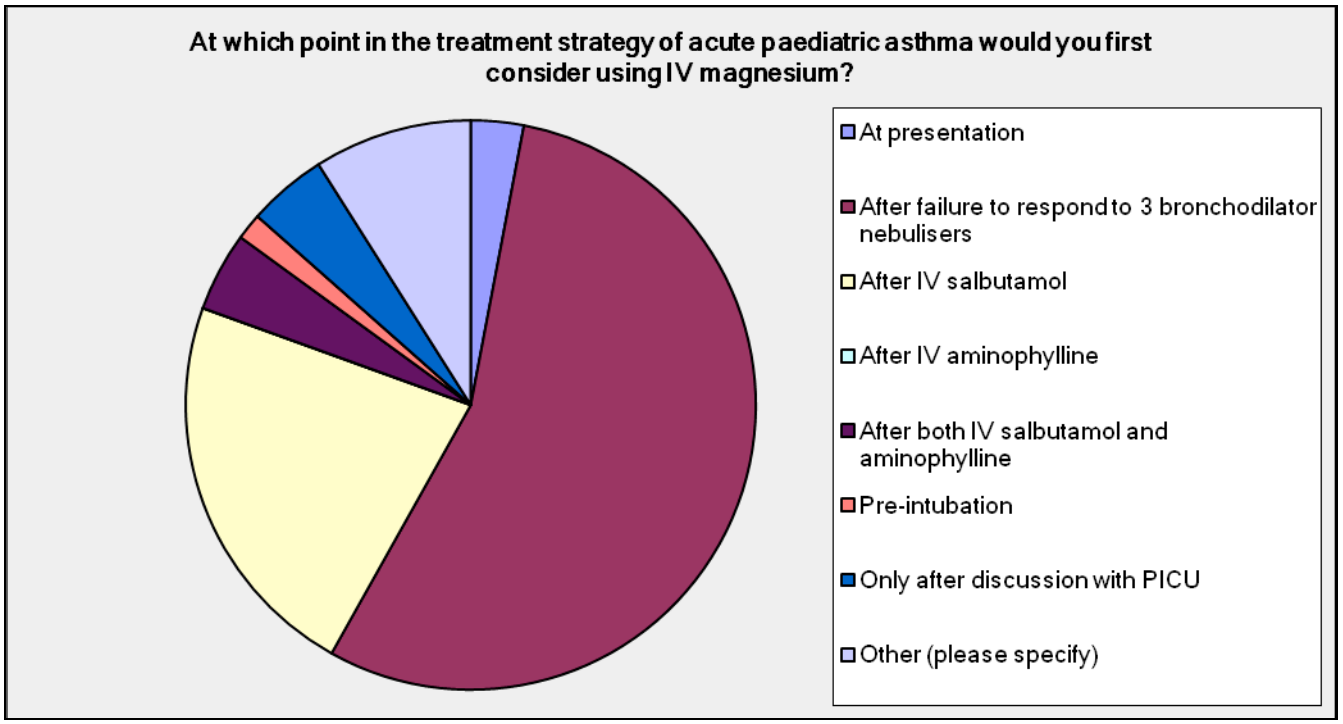
8.Would you consider using IV magnesium in acute paediatric asthma in the future?		
Answer Options	**Response Percent**	**Response Count**
Yes	100.0%	69
No	0.0%	0
answered question		69
skipped question		2



9.At what severity of asthma would you start to consider using IV magnesium in children?		
Answer Options	**Response Percent**	**Response Count**
Mild	0.0%	0
Moderate	3.0%	2
Severe	79.1%	53
Life Threatening	17.9%	12
answered question		67
skipped question		4

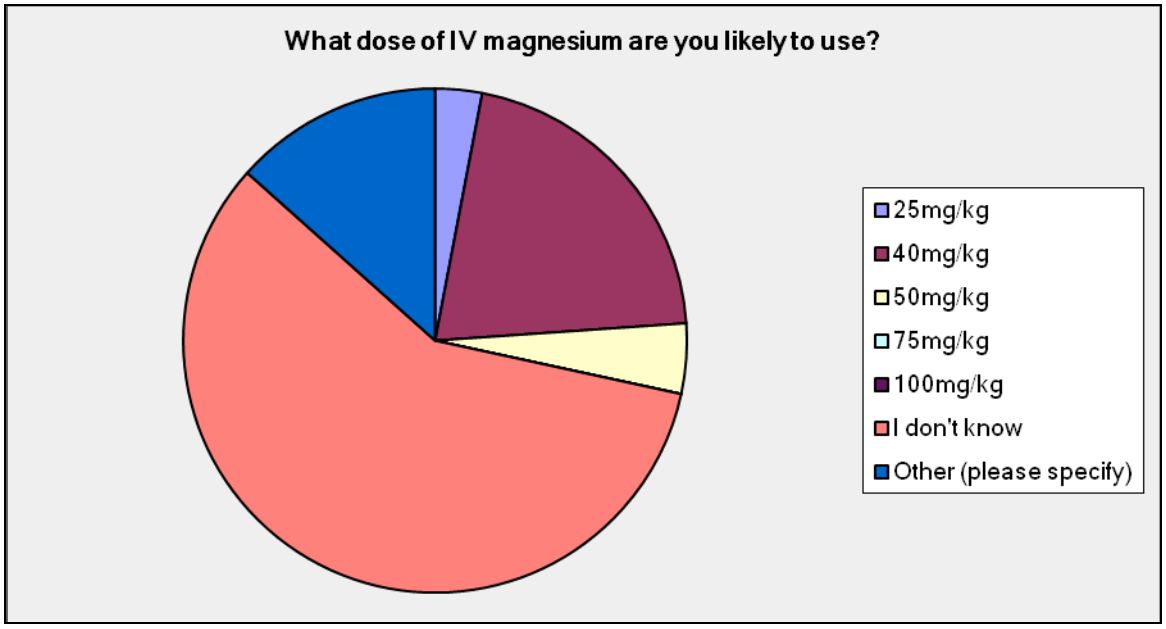


10.At which point in the treatment strategy of acute paediatric asthma would you first consider using IV magnesium?		
Answer Options	**Response Percent**	**Response Count**
At presentation	3.0%	2
After failure to respond to 3 bronchodilator nebulisers	55.2%	37
After IV salbutamol	22.4%	15
After IV aminophylline	0.0%	0
After both IV salbutamol and aminophylline	4.5%	3
Pre-intubation	1.5%	1
Only after discussion with PICU	4.5%	3
Other (please specify)	9.0%	6
answered question		67
skipped question		4



11.What dose of IV magnesium are you likely to use?

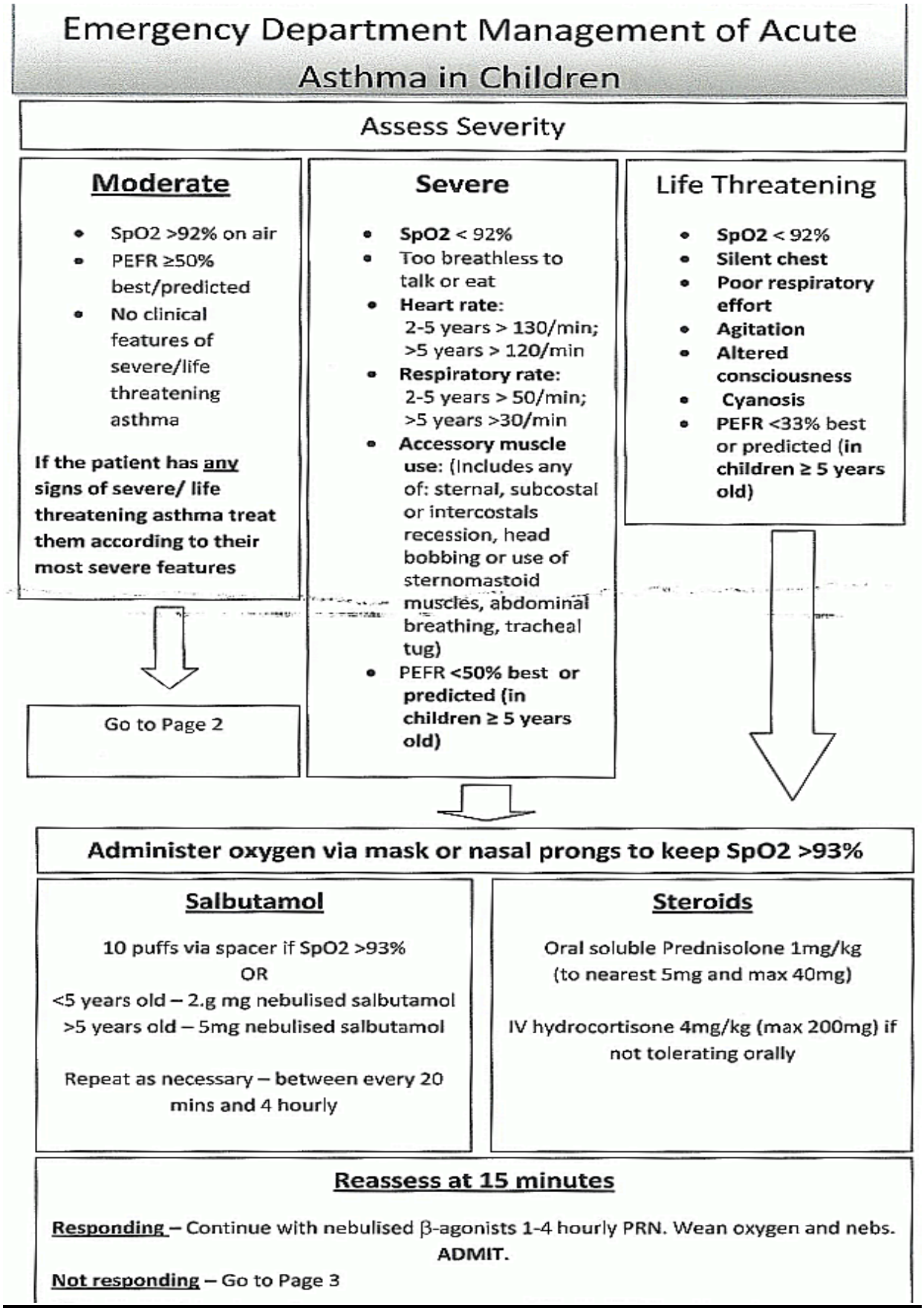
Answer Options	Response Percent	Response Count
25mg/kg	3.0%	2
40mg/kg	20.9%	14
50mg/kg	4.5%	3
75mg/kg	0.0%	0
100mg/kg	0.0%	0
I don't know	58.2%	39
Other (please specify)	13.4%	9
answered question		67
skipped question		4



12.Are there any reasons why you would not use IV magnesium in the future? (You may tick more than one box)

Answer Options	Response Percent	Response Count
No evidence that it is of benefit	0.0%	0
There is evidence of harm	0.0%	0
It is not recommended by BTS/SIGN guidelines	0.0%	0
Other drugs work better	0.0%	0
I can't give a reason	0.0%	0
Other (please specify)	0.0%	0
answered question		0
skipped question		71

Appendix 7. New Departmental Protocol



Management of Moderate Asthma in the Emergency Department

Salbutamol

2 -10 puffs of salbutamol inhaler via spacer

Steroids

1mg/kg oral soluble prednisolone
(to nearest 5mg and max 40mg)

Reassess at 30 – 60 minutes

Responding

Continue inhaled β-agonists 1 – 4 hourly

Potential Discharge

If stable on 4 hourly inhaled β-agonists
Consider the time and home circumstances

- Continue 4 hourly inhaled β-agonists PRN
- 3 day supply of prednisolone
- Check inhaler technique
- Advise GP review if not controlled with above plan
- Provide written action plan
- Review regular medications
- Arrange GP follow up

Not Responding

Reassess severity

No Severe or Life-threatening Features Present

Continue 1 -4 hourly inhaled β-agonists

ADMIT

Severe or Life-threatening Features Present

Go to Page 3

Management of Severe or Life-Threatening Asthma not responding to initial therapy.

Discuss with Senior ED Doctor, Paediatrician or PICU team

ADMIT

Continue with regular nebulised salbutamol every 20 minutes as needed

- <5 years old – 2.5 mg salbutamol
- >5 years old – 5 mg salbutamol

Ipratropium Bromide

- 250mcg nebulised Atrovent 6 hourly
- Can be used up to ½ hourly initially

> 5 years old

<5 years old

Intravenous Magnesium Sulphate

- 40mg/kg bolus (max 2g)
- 100ml volume
- Over 20 minutes

and

Intravenous Salbutamol

- Initial bolus of 15 mcg/kg (max 250mcg) over 10 minutes
- Followed by continuous infusion at 1 – 5 mcg/kg/min

Intravenous Aminophylline

Only to be used if severely ill and not responding to other therapies with mechanical ventilation being contemplated.

- Loading dose – 5mg/kg over 20 minutes (OMIT if on oral theophyllines)
- Maintenance infusion - 1mg/kg/hour

Arrange HDU/PICU admission

- **Intubate and Ventilate in ED if necessary**

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