

Severe Acute Asthma

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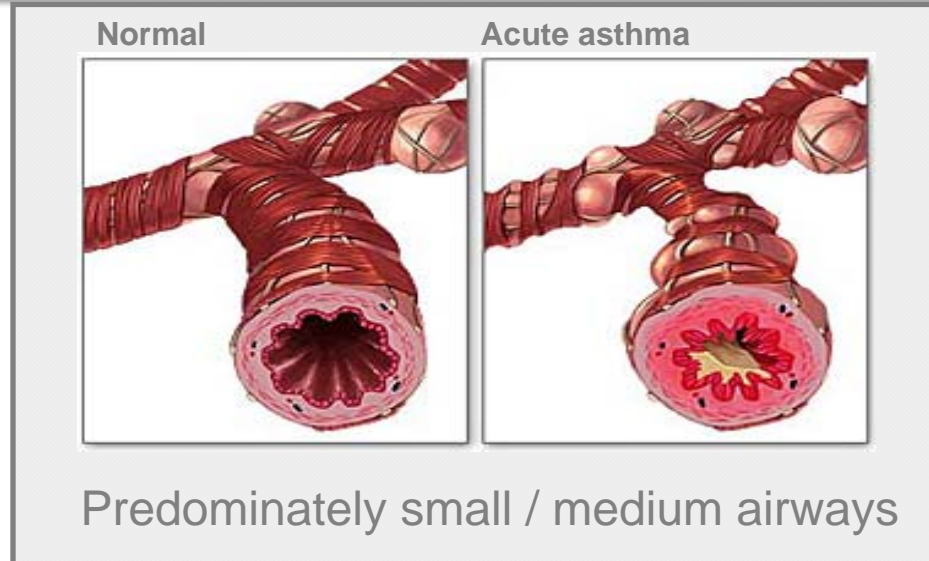


Asthma Pathophysiology

Smooth Muscle Contraction
(bronchospasm)

Airway wall inflammation
& thickening

Excess mucus production



Airway obstruction

Increased work of breathing

Respiratory Muscle Fatigue

V:Q mismatch



CO₂ retention
(alveolar hypoventilation)



Hypoxaemia

**Respiratory
Failure**



Moderate exacerbations

Inhaled β 2 Agonist

Salbutamol - MDI spacer
- 6 puffs / 12 puffs

Systemic Corticosteroids

Oral prednisolone



Severe exacerbations

Oxygen

Inhaled β 2 Agonist

**High dose inhaled
Salbutamol**

(? MDI / Nebuliser)

Inhaled anticholinergic

ipratropium

Corticosteroids

IV methyl prednisolone



Critical exacerbations

Oxygen

Inhaled β 2 Agonist (salbutamol)

Inhaled anticholinergic (ipratropium)

Systemic Corticosteroids (IV methylprednisolone)

Next choice of drug??

IV Aminophylline

IV Magnesium

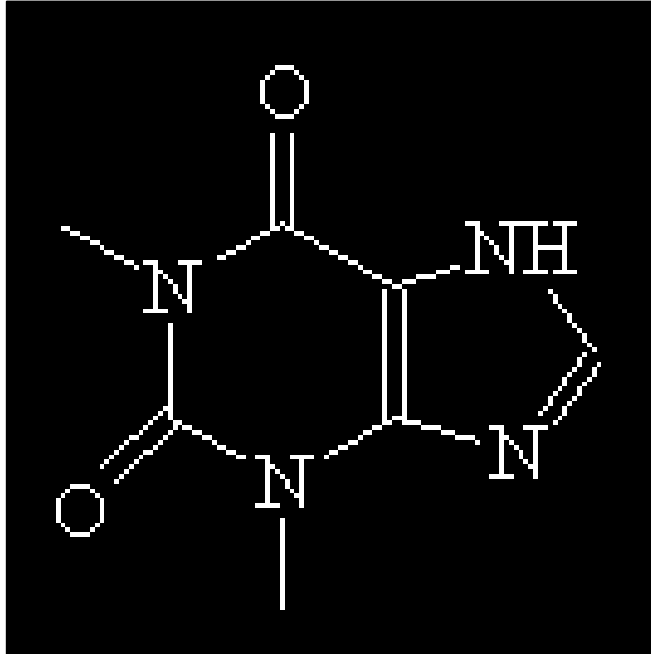
IV β 2 Agonist (salbutamol)

Nebulised Magnesium

IV Montelukast*



Methylxanthines



- Theophylline
- Caffeine
- Theobromine

Coffee / Tea / Chocolate / Cola

Aminophylline

Ethylenediamine salt of Theophylline

CNS Stimulant, Diuretic, Cardiac, Respiratory

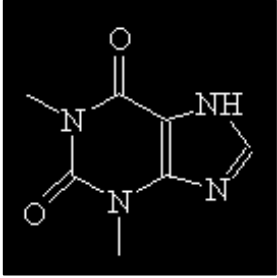


Mechanism of action

- Phosphodiesterase inhibitor
- Transmembrane calcium flux modulation
- Adenosine receptor antagonist
- Enhanced endogenous catecholamine



Actions of Aminophylline



? A perfect drug in asthma

Bronchodilator

Mast cell stabiliser

Respiratory stimulant

Improves respiratory muscle contractility

Cardiac inotrope

Improves Mucocilliary transport

‘The drug with the best documented efficacy in severe acute asthma in children’



William Withering 1741-1799



WILLIAM WITHERING M.D. F. R.S. &c. &c.
*Drawn and Engraved by R. Bead from an original picture
painted by G. F. Benda, in the possession of William Withering Esq. F.R.S.*



History 2

- *Henry Salter 1859*
“One of the commonest and best reputed remedies for asthma is strong coffee”
- *Trendelenberg 1912*
Demonstrated bronchodilator properties of caffeine in cows and humans, and that theophylline was more potent.
- *Herrmann & Aynesworth 1937*
Successful treatment of persistent extreme dyspnea “status asthmaticus” with theophylline ethylene diamine intravenously
- *1950's onward*
Use of aminophylline frequently described in literature
- *1970's*
First “controlled” trials



Paediatric Studies – prior to mid 90's

- 6 RCTs
 - 1 Positive (1970s Isoproterenol)
 - 5 Negative



Study Problems

- Small, low power
- Mild-moderate asthma
(excluded sick/ICU)
- Dose, levels
- Outcomes not very useful



RCH RCT of Aminophylline

Randomised controlled trial of aminophylline for severe acute asthma

Arch Dis Child 1998;79:405–410

Michael Yung, Mike South

What is the role of aminophylline in the modern treatment of asthma?

Do children with SAA unresponsive to frequent doses of beta agonists, ipratropium and steroids benefit from the addition of IV aminophylline?

Hypothesis: No additional benefit





Royal Children's Hospital

Melbourne, Australia



Recent RCH Asthma Review

12 years

32,000 ED attendances

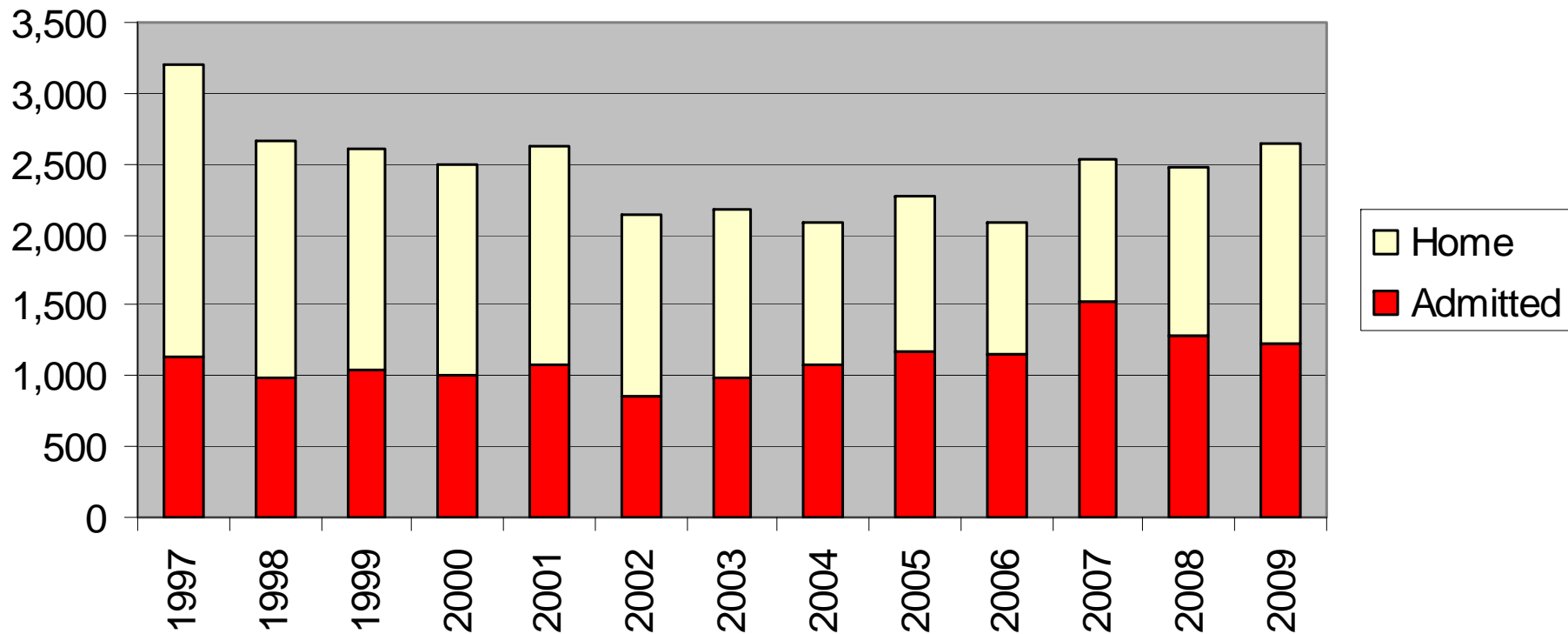
14,000 RCH Admissions

715 ICU admissions

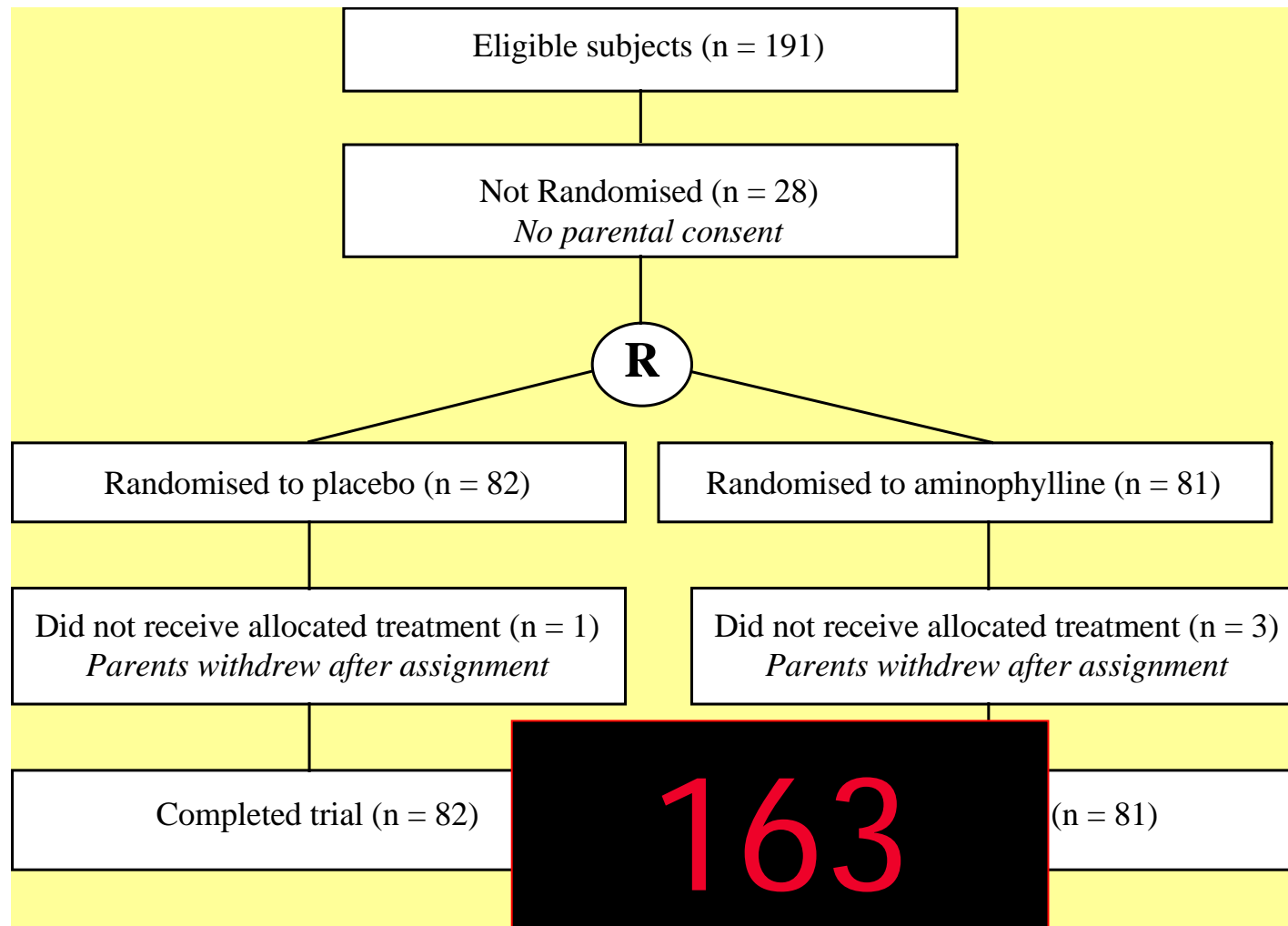


RCH ASTHMA ED ATTENDANCES

Attendances and admissions



Results

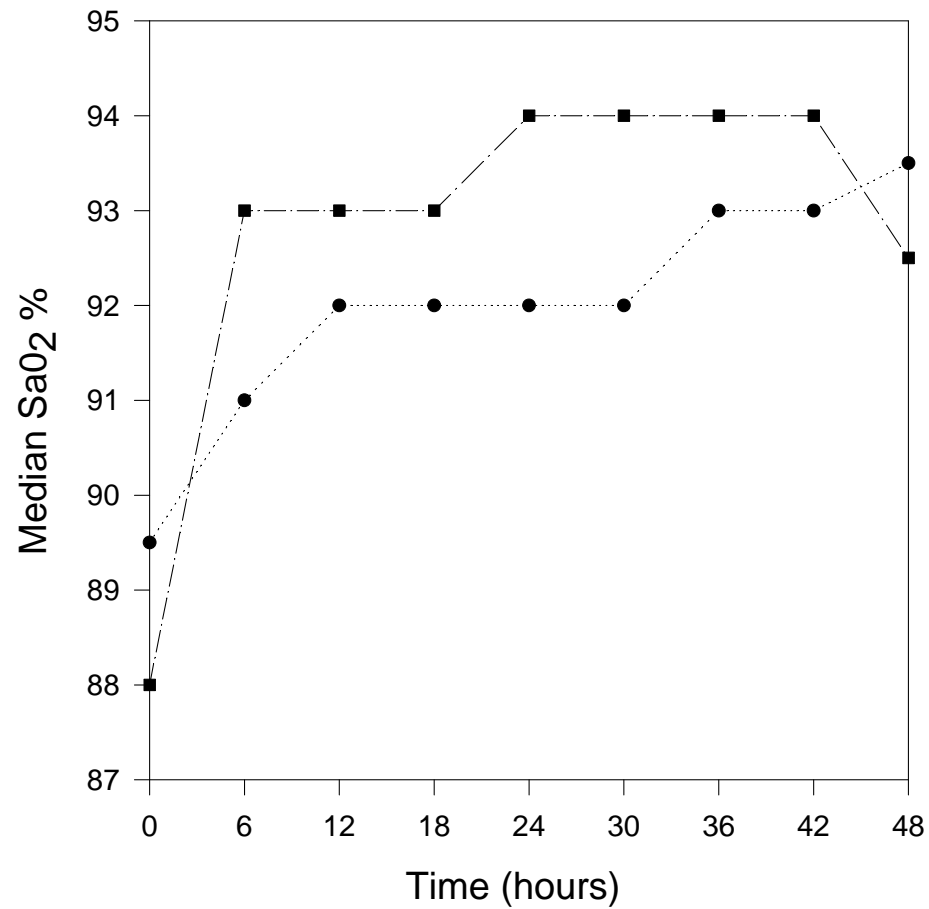


Spirometry

	A	n	P	n	Difference A-P	95%CI for difference	p
<u>FEV₁%</u>							
6h	14.1	25	3.7	17	10.4	(4.2,16.6)	0.0016
12-18h	17.1	19	7.6	16	9.5	(2.6, 16.3)	0.0082
24h	22.5	22	13.1	17	9.4	(1.0, 17.9)	0.029
<u>MMEF%</u>							
6h	13.3	25	-0.4	17	9.3	(4.3, 15.7)	0.0016
12-18h	13.2	19	6.9	16	6.3	(0.3, 12.3)	0.041
24h	17.1	22	11.6	17	5.5	(-3.0, 14.1)	0.2
<u>PEFR%</u>							
6h	14.8	25	-0.3	17	15.1	(6.5, 23.7)	0.001
12-18h	16.6	19	6.3	16	10.3	(1.7, 18.9)	0.02
24h	22.4	22	12.2	17	10.2	(0.3, 19.9)	0.043



SaO₂ in air for 5 minutes



Other outcomes

	Aminoph	Placebo	p
LOS (d)	2.68	2.87	0.53
O2 duration (h)	6	18	0.015
AS Score (@6H)	5.6	6.2	0.032
IV salbutamol (%)	18	32	0.03
IV salbutamol (duration)	8.8	16	0.045
new IPPV (%)	0	6.6	0.027
duration IPPV (h)	8.25	34	0.087
Nausea (%)	66	23	0.0004
Vomiting (%)	67	19	0.0001

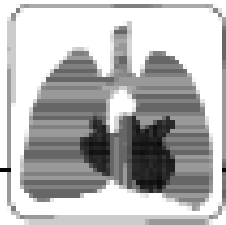


Summary

- No effect on length of stay
- Improved clinical scores,
- Improved spirometry, SaO₂
- Less O₂, IV salbutamol
- Less need for IPPV (risk & duration)
- Nausea & vomiting.

~~Hypothesis: No additional benefit~~





clinical investigations in critical care

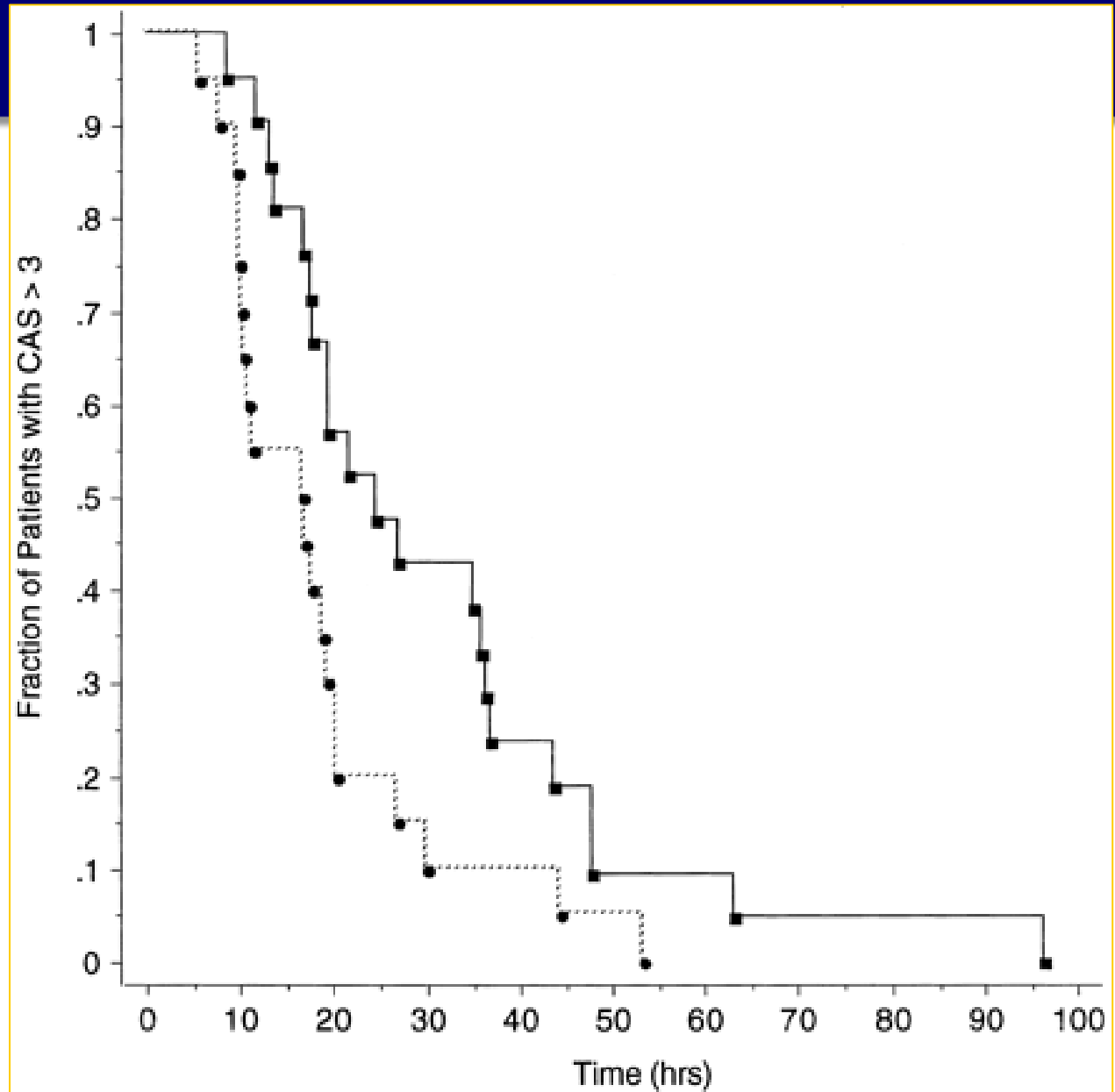
Efficacy of IV Theophylline in Children With Severe Status Asthmaticus*

*Robert S. Beam, MD; Laura L. Loftis, MD; Gary M. Albers, MD;
Bradley A. Becker, MD; Robert E. Lynch, MD, PhD; Richard B. Mink, MD*

Chest 2001;119:1480-1488



Results



Results INTUBATION

Placebo 15%

Aminophylline 0%



Conclusions

Aminophylline effective

? IV salbutamol or IV aminophylline



Salbutamol IV

The Cochrane Database of Systematic Reviews

The Cochrane Library, Copyright 2001, The Cochrane Collaboration

Volume (Issue 3) 2001 [no page #]

Intravenous beta2-agonists for acute asthma in the emergency department

[Review]

Travers, A; Jones, AP; Kelly, K; Barker, SJ; Camargo, Jr CA; Rowe, BH

Conclusions

There is no evidence to support the use of IV beta2-agonists in patients with severe acute asthma.

These drugs should be given by inhalation.

No subgroups were identified in which the IV route should be considered.

Limitations

Drug Levels



Salbutamol IV

Paediatric studies

An insufficient number of pediatric papers with similar outcome measures were identified and this precluded any subgroup comparison on the basis of age. Only three of the fifteen included papers evaluated the pediatric population

([Browne 1997](#); [Hussein 1986](#); [Hambleton 1979](#)).



IV Salbutamol vs Aminophylline

G Roberts et al.

Intravenous salbutamol bolus compared with an aminophylline infusion in children with severe asthma: a randomised controlled trial. Thorax. 2003

Aminophylline group had:

- Faster improvement in severity score
- Shorter LOS
- 4% vs 11% intubation rate (ns)

44 patients



Conclusion

- Aminophylline works but beware toxicity
- IV Salbutamol may work but no very good evidence
- Evidence suggesting aminophylline is more effective



Magnesium

- Reduces excitability of smooth muscle membrane
 - Competes for Ca^{2+} uptake in smooth muscle
 - Inhibits acetylcholine release
- Inhibits mast cell degranulation



A meta-analysis on intravenous magnesium sulphate for treating acute asthma

D K L Cheuk, T C H Chau, S L Lee

KIDS

A Meta-analysis on Intravenous Magnesium Sulphate for Treating Acute Asthma

John M. Kelso, MD

PEDIATRICS Vol. 118 Supplement August 2006, pp. S45-S46 (doi:10.1542/peds.2006-0900XXX)

- Five trials 182 patients
- Reduced hospitalisation
- Small improvement in lung function
- Nothing on ICU outcomes
- Probably safe



Inhaled magnesium sulfate in the treatment of acute asthma

M Blitz, S Blitz, R Beasley, BM Diner, R Hughes, JA Knopp, BH Rowe

Cochrane Database of Systematic Reviews 2007 Issue 2

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- 6 studies ~300pts (4 adult, 2 paed)
- Modest benefits in lung function (mostly ns trends)
- Appear additive with B Agonists
- No clear benefit for important outcomes
- Needs more study



ORIGINAL ARTICLE

Intravenous and nebulised magnesium sulphate for acute asthma: systematic review and meta-analysis

S Mohammed, S Goodacre



This paper is freely available online under the BMJ Journals unlocked scheme, see <http://emj.bmj.com/info/unlocked.dtl>

Objectives: To estimate the effect of intravenous and nebulised magnesium sulphate upon hospital admissions and pulmonary function in adults and children with acute asthma.

Methods: We undertook a systematic review and meta-analysis of randomised and quasi-randomised trials of intravenous or nebulised magnesium sulphate in acute asthma. Trials were identified by searches of the electronic literature, relevant journal websites and conference proceedings, and contact with authors and experts. Data were pooled using random effects meta-analysis of the relative risk (RR) of hospital admission and the standardised mean difference (SMD) in pulmonary function.

Results: 24 studies (15 intravenous, 9 nebulised) incorporating 1669 patients were included. Intravenous treatment was associated in adults with weak evidence of an effect upon respiratory function (SMD 0.25, 95% confidence interval (CI) -0.01 to 0.51; $p=0.05$), but no significant effect upon hospital admission (RR 0.87, 95% CI 0.70 to 1.08; $p=0.22$), and in children with a significant effect upon respiratory function (SMD 1.94, 95% CI 0.80 to 3.08; $p<0.001$) and hospital admission (RR 0.70, 95% CI 0.54 to 0.90; $p=0.005$). Nebulised treatment was associated in adults with weak evidence of an effect upon respiratory function (SMD 0.17, 95% CI -0.02 to 0.36; $p=0.09$), and hospital admission (RR 0.68, 95% CI 0.46 to 1.02; $p=0.06$), and in children with no significant effect upon respiratory function (SMD -0.26, 95% CI -1.49 to 0.98; $p=0.69$) or hospital admission (RR 2.0, 95% CI 0.19 to 20.93; $p=0.56$).

Conclusion: Intravenous magnesium sulphate appears to be an effective treatment in children. Further trials are needed of intravenous and nebulised magnesium sulphate in adults and nebulised magnesium sulphate in children.



Prof Mike South

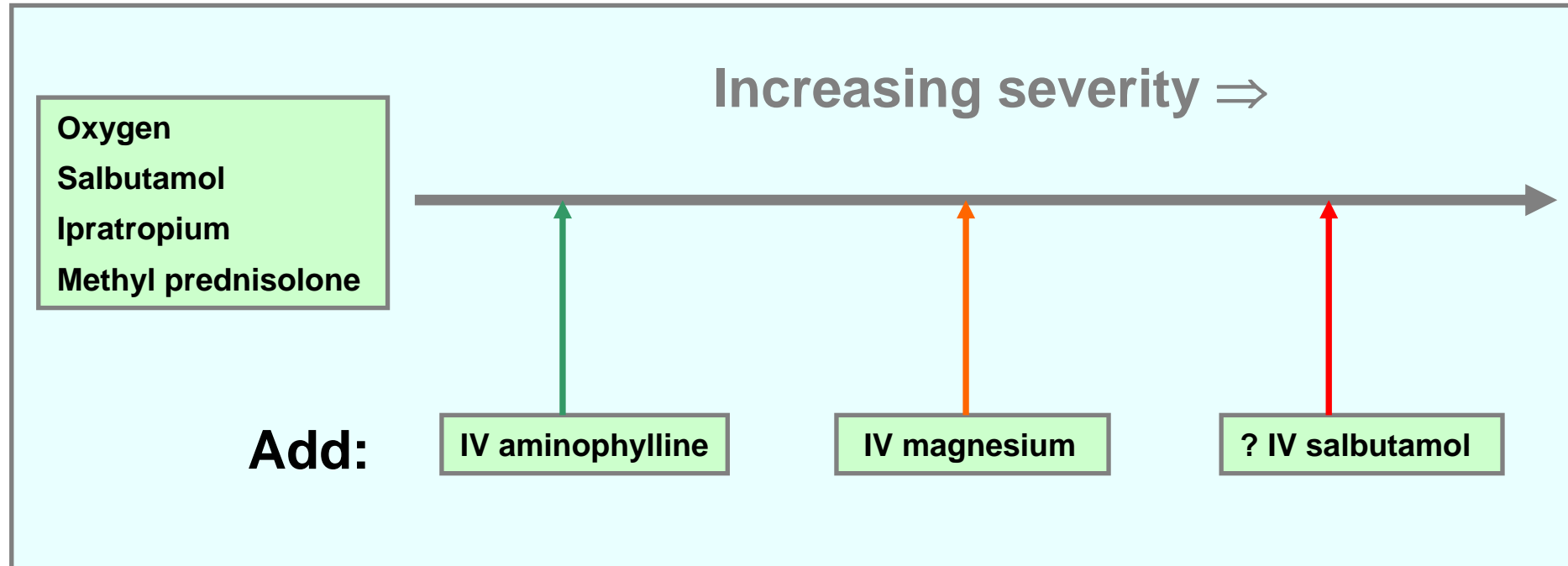
Severe Acute Asthma

Magnesium for SAA in children

- May be helpful
- Probably safe
- Cheap



Drug therapy: severe \Rightarrow critical exacerbations



The forgotten treatment

Simple

Inexpensive

Non-Toxic

Very effective



The forgotten treatment

Patience

Often bronchospasm is reversed but obstruction persists due to airway inflammation, oedema, & mucus.

Natural recovery plus anti-inflammatory effects of steroids take time.

Tempting to continue escalating bronchodilators
Do not rush to do so if patient is coping.(toxicity)

Reassurance of patient / family / staff very important.



Why is the SaO₂ low in acute asthma?

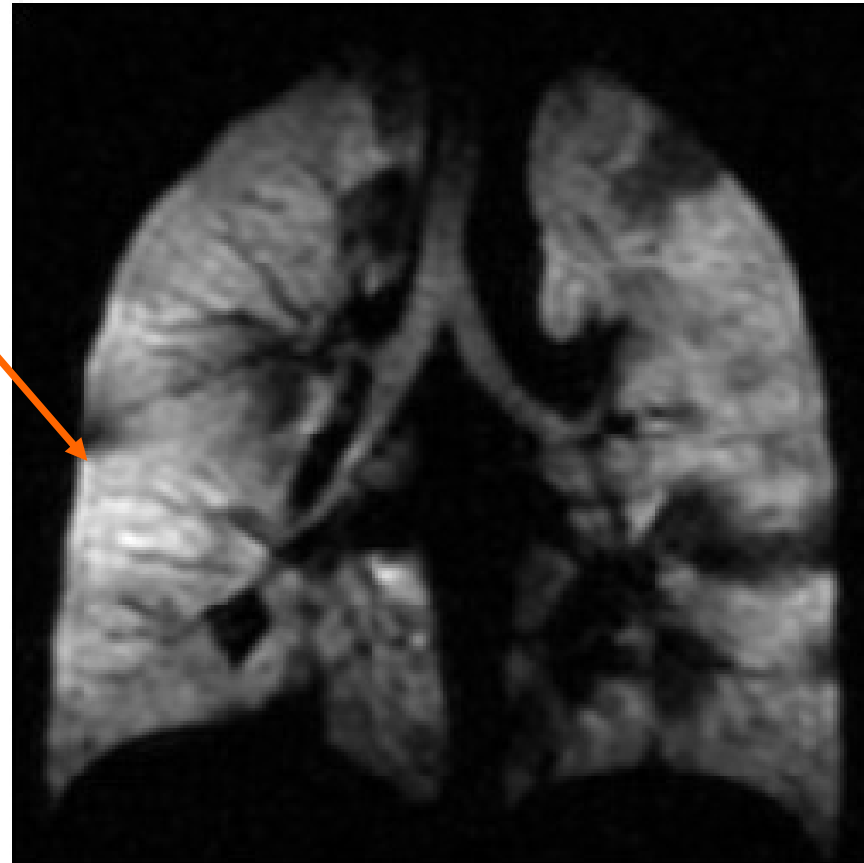
Hyperpolarized helium (He 3) Ventilation MRI

Normal

V:Q mismatch.

Can occur in moderate asthma.

Beware of over-treatment based on SaO₂.



Non-invasive mechanical ventilatory support

Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma (Review)

Ram FSE, Wellington SR, Rowe B, Wedzicha JA

Cochrane Database of Systematic Reviews 2005, Issue 3. Art. No.: CD004360. DOI:

Case series evidence
One small trial
No ICU outcomes
We have been using -
looks promising



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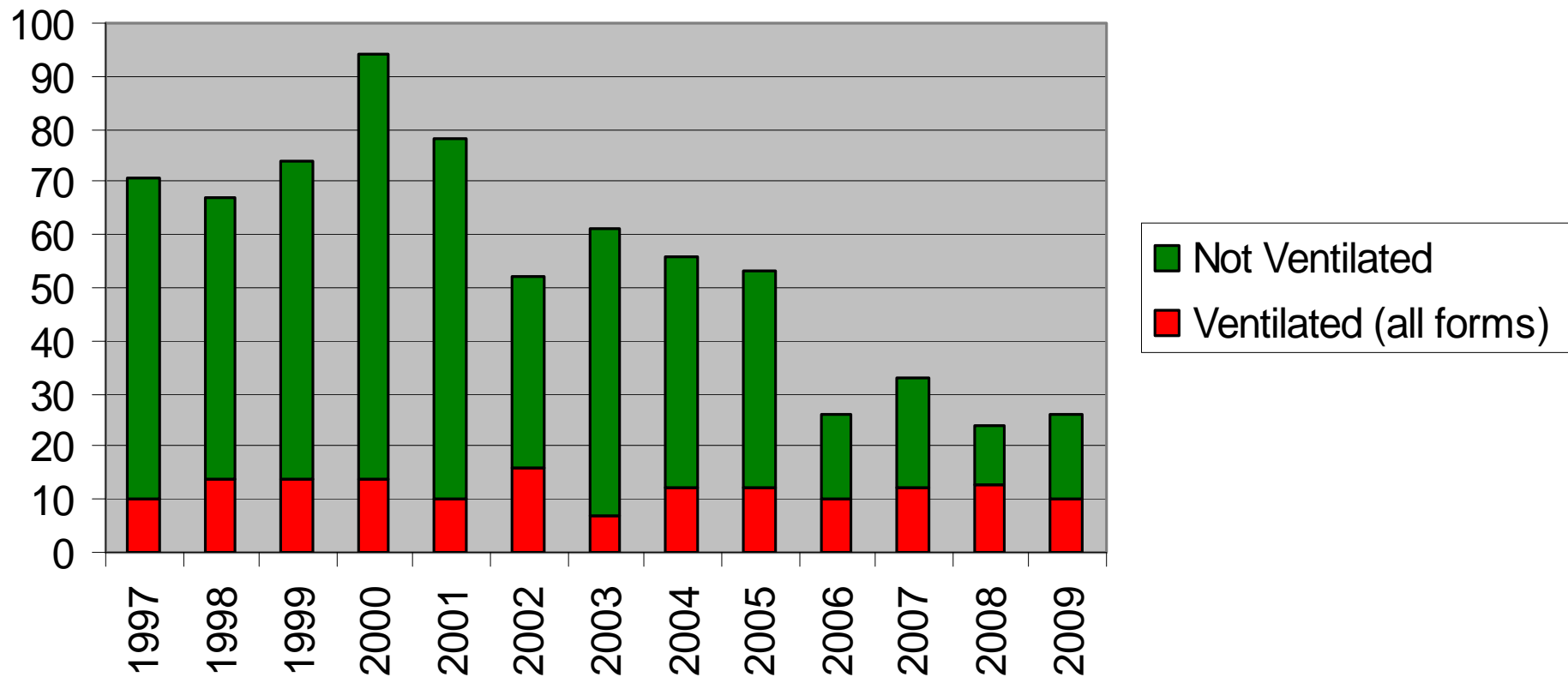
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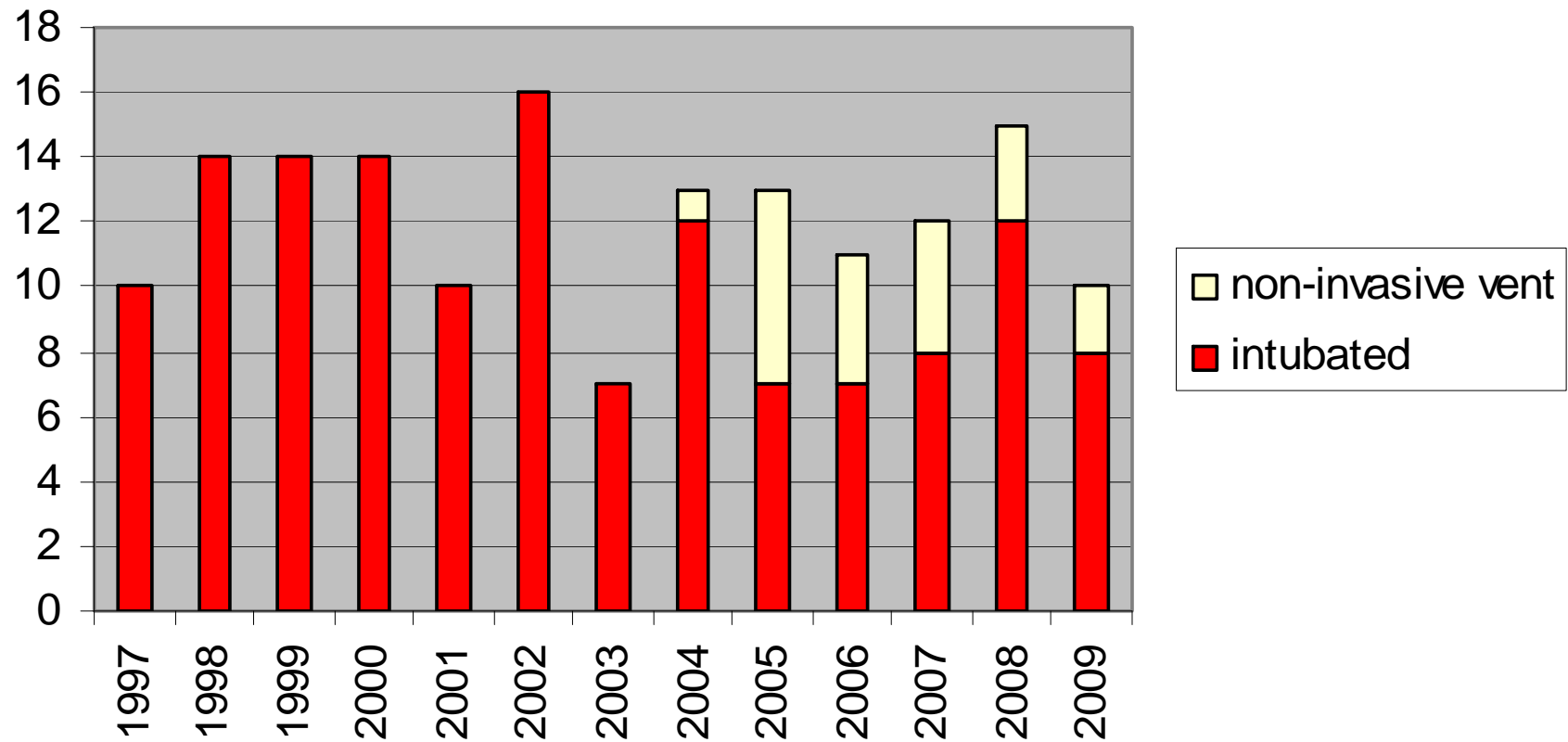
RCH ICU - ADMISSIONS & VENTILATION

ICU admissions

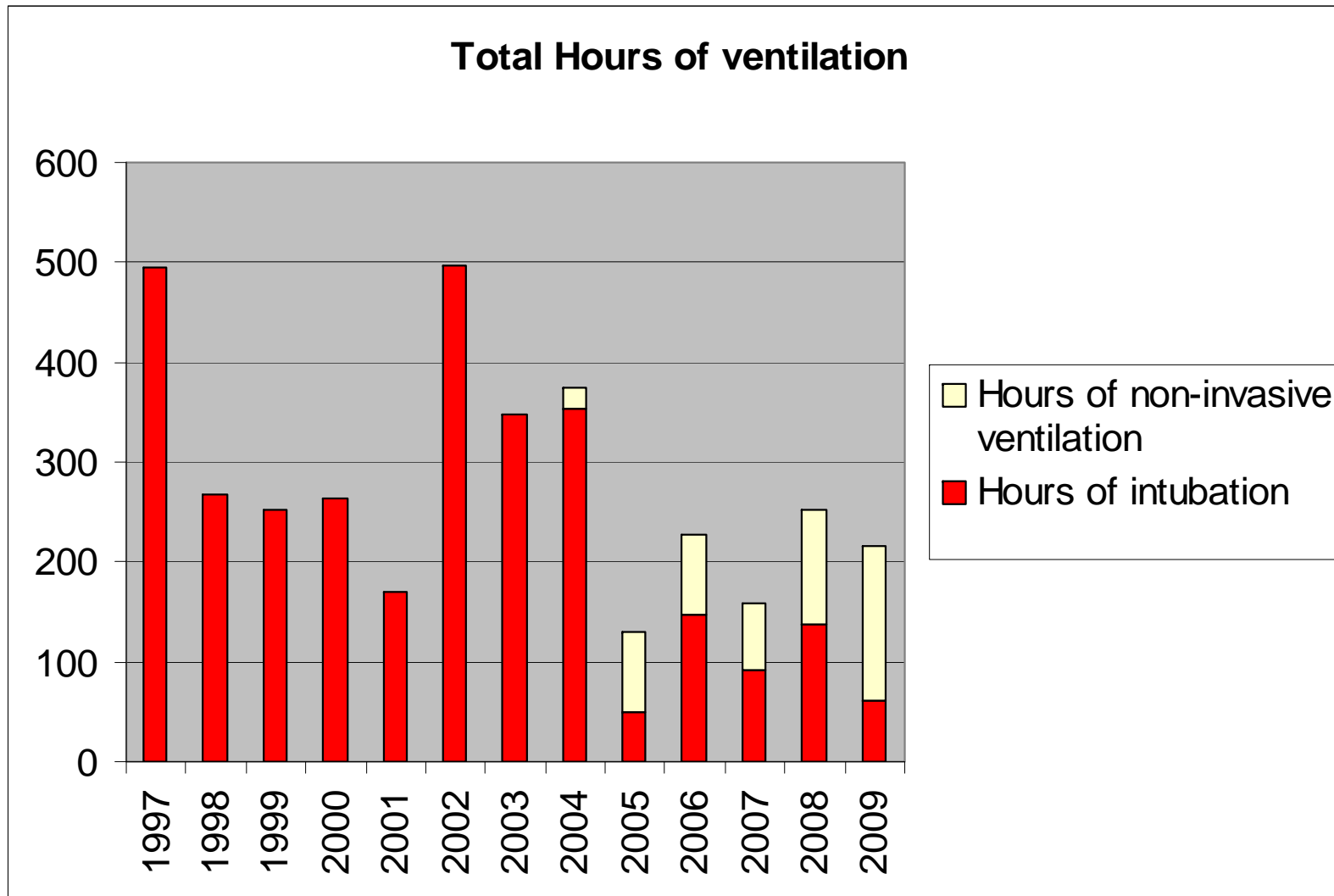


RCH ICU - VENTILATED FOR ASTHMA

Number of Patients Ventilated

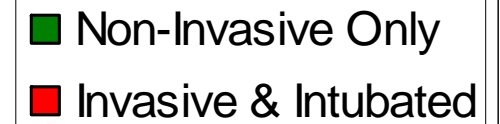
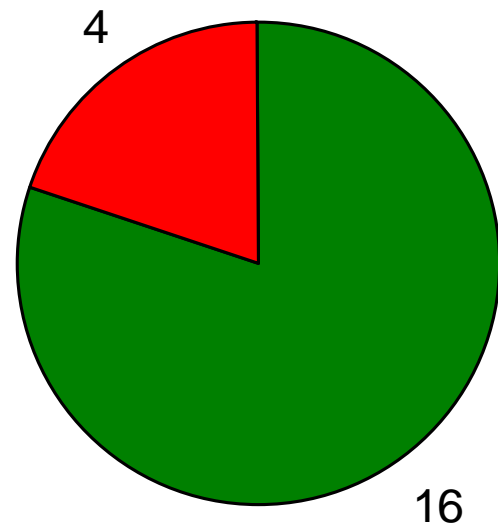


RCH ICU - HOURS OF VENTILATION FOR ASTHMA



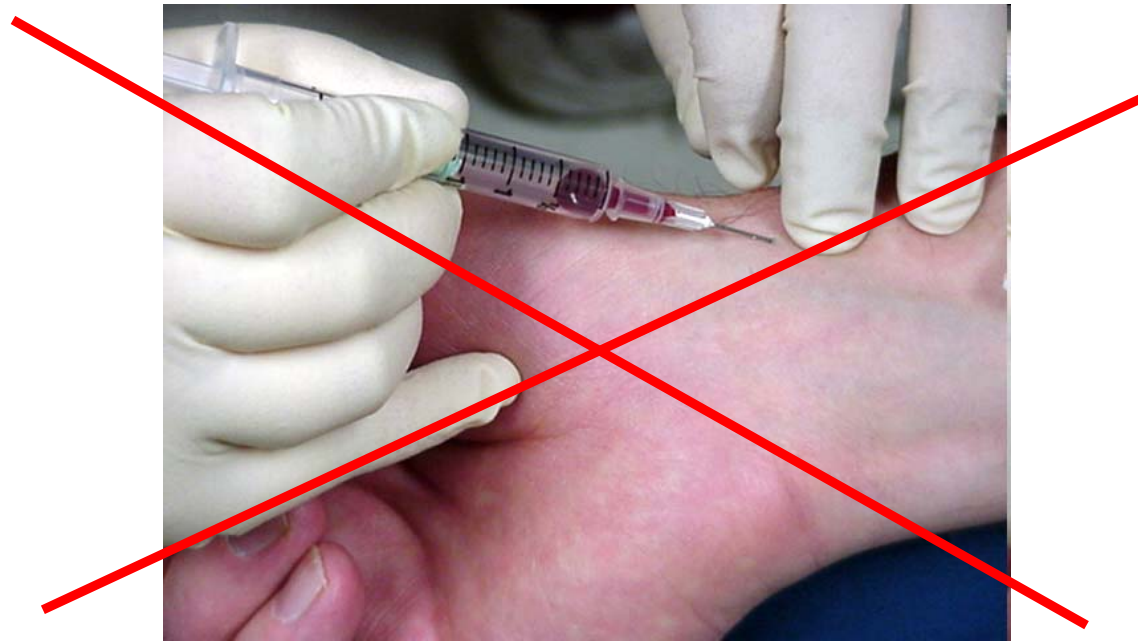
RCH ICU - VENTILATION FOR ASTHMA

Non-Invasive Ventilation

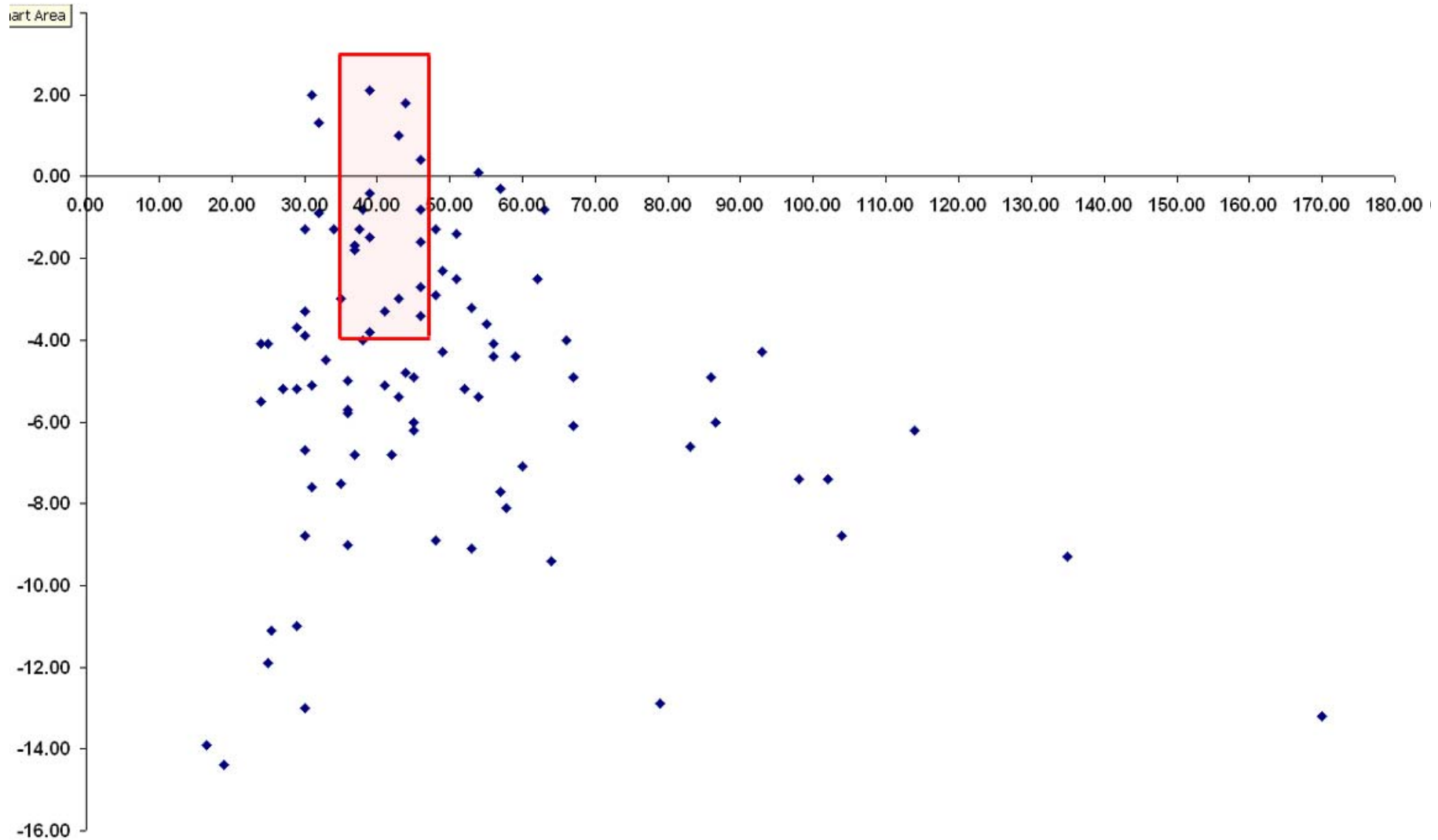


Acid Base Disturbance in Acute Asthma

- I never take an arterial blood gas!
- Venous blood for lactate - sometimes



Acid Base Disturbance in Acute Asthma



Acid Base Disturbance in Acute Asthma

66% acidaemia (pH <7.35)

86% metabolic component (BE < -5.0)

Metabolic acidosis predominantly due to high lactate



Lactic Acidosis in Acute Asthma

Possible causes

- Tissue hypoxaemia / anaerobic metabolism
- Increased respiratory work / anaerobic metabolism
- Circulatory failure
- Reduced lactate clearance
- **Drugs - salbutamol**



Salbutamol Acidosis in Acute Asthma

- β 2 agonist - like adrenaline
- Stimulates muscle & liver glycogenolysis and gluconeogenesis - raises blood sugar rapidly.
- Generates lactate



Salbutamol Acidosis in Acute Asthma

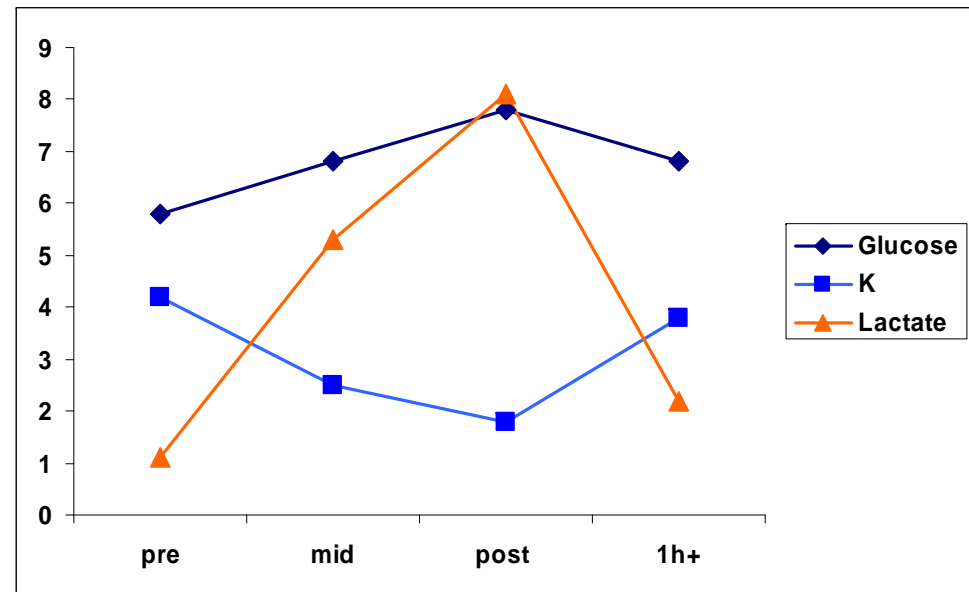
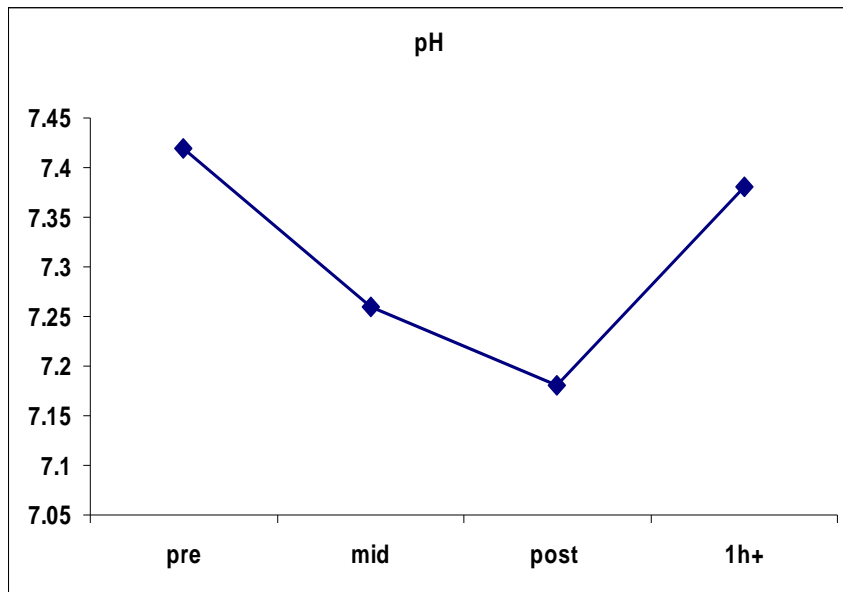
- Several children in our study had immediate improvements in RR, acidosis and general condition when salbutamol ceased.
- Plan to study adult volunteers



1 hour of inhaled salbutamol in a healthy adult



1 hour of inhaled dilute salbutamol in a healthy adult



Near death experience



Consider salbutamol toxicity

- significant tachypnoea and little retraction or wheeze
- not improving as expected despite appropriate therapy
- metabolic acidosis
- younger
- Presence of signs of bronchoconstriction does not exclude salbutamol toxicity

Try cessation of salbutamol for 1 hour



Salbutamol Acidosis in Acute Asthma

Metabolic acidosis as an underlying mechanism of respiratory distress in children with severe acute asthma*

Kathleen L. Meert, MD, FCCM; Jeff Clark, MD; Ashok P. Sarnaik, MD, FCCM



- About RCH CPG's
- Guideline index
- Mailing lists
- Feedback

Asthma (Acute)

- [Click here for other resources](#)

RCH Research study in progress - Lung function in pre-school wheezing [click here](#) to read more

Assessment and Management

Severity	Signs of Severity	Management
Mild	<p>Primary</p> <p>Normal mental state</p> <p>Subtle or no accessory muscle use/recession</p> <p>Secondary</p> <p>= O₂ saturation > 95% in air</p> <p>Able to talk normally</p>	<p>Salbutamol by MDI/spacer* - once and review after 20 mins. Ensure device / technique appropriate.</p> <p>Good response - discharge on B2-agonist as needed.</p> <p>Poor response - treat as moderate.</p> <p>Oral prednisolone (1 mg/kg daily for 1-3 days) if on prophylaxis or episode has persisted over several days.</p> <p>Provide written advice on what to do if symptoms worsen. Consider overall control and familyxs knowledge. Arrange follow-up as appropriate.</p> <p>(discharge pack)</p>
Moderate	<p>Primary</p> <p>Normal mental state</p> <p>Some accessory muscle use/recession</p> <p>Secondary</p> <p>= O₂ saturation 92-95% in air</p> <p>Tachycardia</p> <p>Some limitation of ability to talk</p>	<p>Give O₂ if O₂ saturation is < 92%. Need for O₂ should be reassessed.</p> <p>Salbutamol by MDI/spacer - 1 dose* every 20 minutes for 1 hour ; review 10-20 min after 3rd dose to decide on admission or discharge.</p> <p>Oral prednisolone (1 mg/kg daily for 3 days)</p> <p>The few children of moderate severity who can go home must be discussed with the registrar and should not leave Emergency until at least one hour after their last nebuliser. Arrange home treatment and follow-up as above.</p>

LINK

Conclusion

Have a structured approach to drug therapy

IV aminophylline

IV magnesium

? IV salbutamol

Don't treat the SaO2 monitor

Be vigilant - drug side effects

especially salbutamol

consider reducing therapy

Be patient – benefits of steroids & time

Consider face-mask CPAP

www.mikesouth.org.au



Invasive mechanical ventilatory support

Rarely needed now.

- Ketamine
- Tube size / cuff
- Pressure-controlled
- 16 breaths/minute
- PEEP 5-10 cm
- PIP - chest movement
- IT 0.8



- Permissive hypercapnoea - 70mmHg
- SaO₂ - accept 85-90% in 70% O₂
- Beware hypovolaemia
- Beware failure to ventilate
- Manual lateral chest compression



Other therapies - case series evidence only

Heliox - reduced gas viscosity

Nebulised DNase
Deoxyribonuclease - mucolysis

Ketamine - bronchodilator

Volatile
anaesthetics - bronchodilator
eg Halothane
? sevoflurane



- The adverse effects of parenterally administered Magnesium usually are the result of Magnesium intoxication. These include flushing, sweating, hypotension, depressed reflexes, flaccid paralysis, hypothermia, circulatory collapse, cardiac and central nervous system depression proceeding to respiratory paralysis. Hypocalcemia with signs of tetany secondary to Magnesium sulfate therapy for eclampsia has been reported.

Read more:

<http://www.drugs.com/pro/magnesium.html#ixzz0vtcXwOxG>

