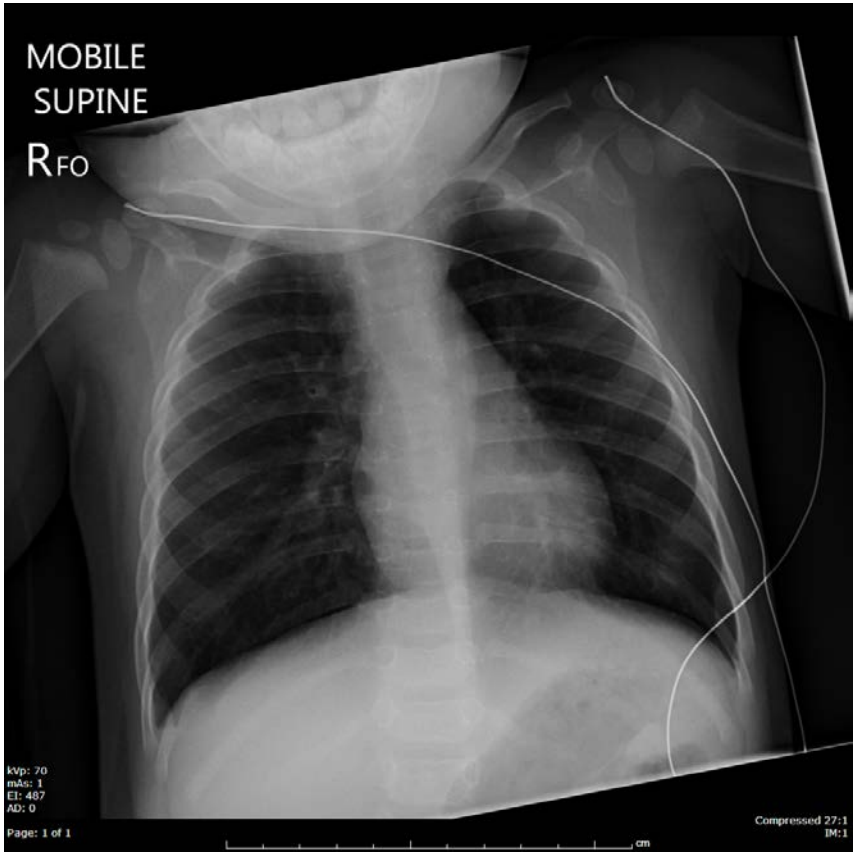
The DAB trial

Background

- What is bronchiolitis?
- Lower respiratory tract infection preceded by cough coryza and fever
- Followed by dyspnoea cough wheeze
- Tachypnoea and hyperinflation of the chest are common features
- Wheezing in a child less than 24 months of age with symptoms and signs of viral illness
- Peak incidence 2-6 months
- Almost all infants are infected by RSV by the end of their second winter and half are re-infected
- Virus induced wheezing, atopic asthma and bronchiolitis overlap
- Pathology is inflammation oedema and necrosis in the small airways
- RSV and rhinovirus are the most common viruses
- Human metapneumovirus, parainfluenza 3, influenza adenovirus
- Co-viral infection in up to 30%

Background

- RSV – ubiquitous worldwide organism
- Seasonal outbreaks
- Worldwide it starts in autumn and peaks in winter
- Incubation period 3-4 days
- Spread by fomites ie large droplet spread from hand contact
- Not respiratory transmission



Background

- US figures 17 year hospital discharge survey
- 1.65 M hopitalisations for bronchiolitis
- 81% less than 1 year of age
- Median hospital LOS 3 days
- Hospitalisation doubled from 13/1000 to 31/1000 over the period
- Risk factors for severe disease
  - Prematurity
  - LBW
  - Age less than 12 weeks
  - Chronic lung disease congenital heart disease
  - Neurological disease
  - Immunodeficiency
  - Congenital airway defects

All respiratory support by year (RCH)

	2005	2006	2007	2008	2009	2010	2011	2012	total
ett	24	36	32	51	13	37	33	23	249
HFNP							58	109	167
Mask		18		1	1	2	36	2	60
NP				1	1	1	7		10
NCPAP	65	75	73	50	44	47	63	36	453

Admissions LOS and respiratory support (RCH)

	admits	Avg PICU LOS (hrs)	Avg hours resp support (all)(hrs)
2005	82	95.06	75.84
2006	102	96.38	77.92
2007	72	88.33	67.90
2008	61	122.56	106.15
2009	61	79.46	61.68
2010	63	92.40	64.43
2011	108	108.16	81.99
2012	107	84.22	56.60

Therapy and the evidence

- Oxygen
- Feeding
- Respiratory support
- Steroids – nebulised oral and systemic
- Adrenaline
- Heliox
- Antivirals
- Other nebulised therapy
  - Salbutamol, ipratropium
  - Hypertonic saline
- Combinations

The prelude to the DAB trial

ORIGINAL ARTICLE

Epinephrine and Dexamethasone in Children with Bronchiolitis

Amy C. Plint, M.D., M.Sc., David W. Johnson, M.D., Hema Patel, M.D., M.Sc., Natasha Wiebe, M.Math., Rhonda Correll, H.B.Sc.N., Rollin Brant, Ph.D., Craig Mitton, Ph.D., Serge Gouin, M.D., Maala Bhatt, M.D., M.Sc., Gary Joubert, M.D., Karen J.L. Black, M.D., M.Sc., Troy Turner, M.D., Sandra Whitehouse, M.D., and Terry P. Klassen, M.D., M.Sc., for Pediatric Emergency Research Canada (PERC)

The prelude to the DAB trial

- Multicentre RCT
- 8 Canadian EDs
- 800 infants 6weeks to 12 months
- Four study groups
  - 2 treatments of nebulised adrenaline 3ml of 1/1000 and 6 oral doses of dexamethasone 1mg/k followed by 0.6mg/k oral daily
  - Nebulised adrenaline and oral placebo
  - Nebulised placebo and oral dexamethasone
  - Nebulised placebo and oral placebo

- Primary outcome – hospital admission within 7 days after enrolment
- Secondary outcomes
  - Clinical respiratory parametres within 6 hours
  - Length and severity of symptoms
  - Time to discharge
  - Rate of representation to health care within 22 days

The prelude to the DAB trial

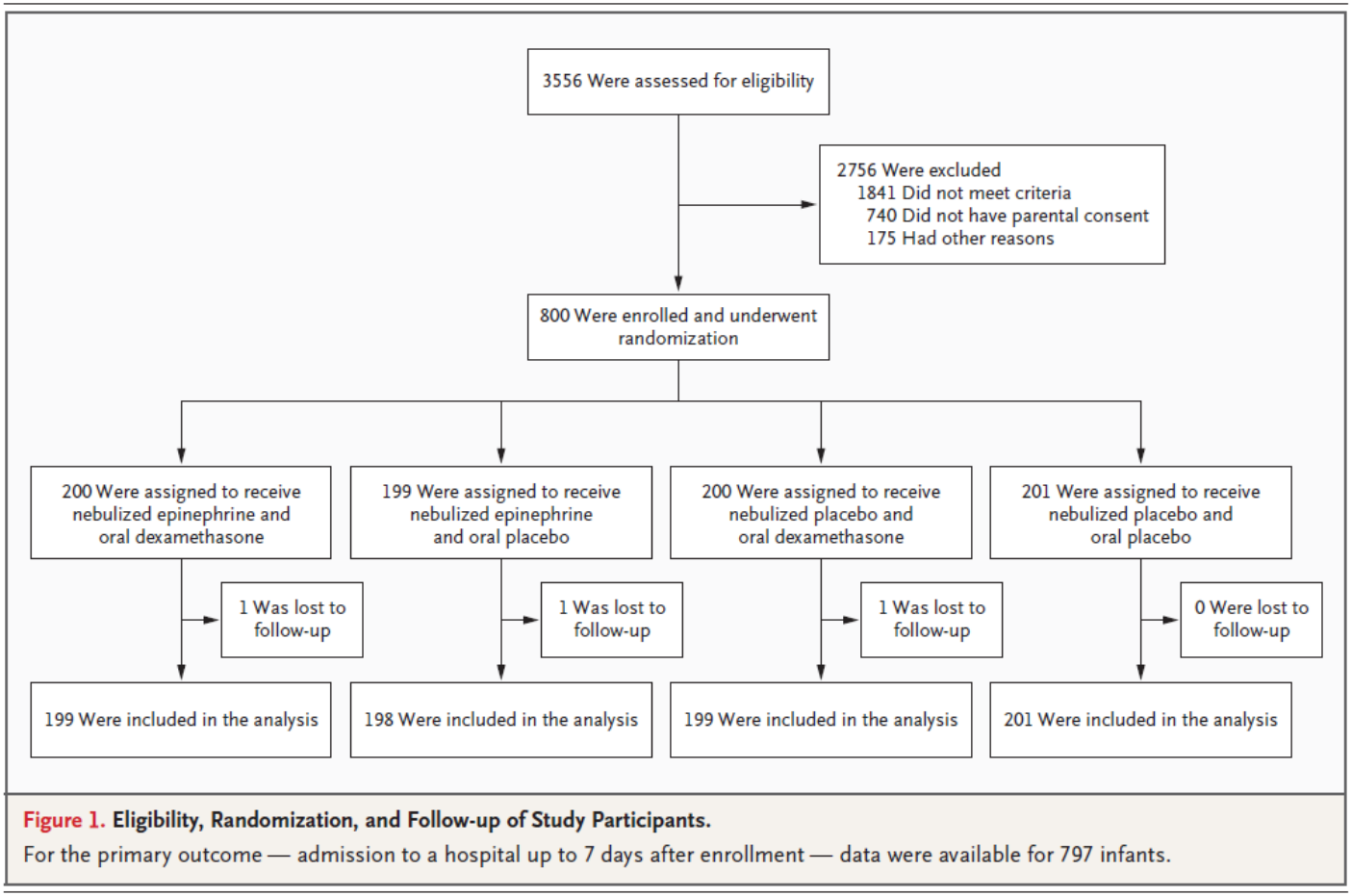


Figure 1. Eligibility, Randomization, and Follow-up of Study Participants.
For the primary outcome — admission to a hospital up to 7 days after enrollment — data were available for 797 infants.

The prelude to the DAB trial

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Epinephrine–Dexamethasone Group (N=200)	Epinephrine Group (N=199)	Dexamethasone Group (N=200)	Placebo Group (N=201)
Age — mo				
Median	5	5	5	5
Interquartile range	3–7	3–7	3–7	3–7
Male sex — no. (%)	124 (62.0)	122 (61.3)	127 (63.5)	120 (59.7)
Clinical characteristics				
RDAI score				
Median	8	8	8	8
Interquartile range	6–10	6–10	6–10	6–10
Respiratory rate — breaths/min				
Median	48	48	50	48
Interquartile range	41–57	44–56	44–60	40–58
Heart rate — beats/min				
Median	150	149	152	150
Interquartile range	138–160	138–160	141–161	137–160
Oxygen saturation — %				
Median	97	97	97	97
Interquartile range	95–98	95–98	95–98	95–98

The prelude to the DAB trial

- **Results**
- Group 1 compared to group 4 RR 0.65 (0.45-0.95 p = 0.02)
- Unadjusted reached significance whereas the adjusted RR did not
- NNT 11 infants to prevent 1 hospital admission
- Hospitalisation decreased by 9.3%
- Significance lost when adjusted for comparisons
- Secondary outcomes
- Earlier discharge from medical care
- Faster return to normal feeding
- Neither adrenaline alone or dexamethasone alone had an outcome effect

The prelude to the DAB trial

Admission	No. of Patients (%)	Relative Risk (95% CI)	95% CI (adjusted)
At enrollment			
Placebo	36 (17.9)	1.00	
Epinephrine and dexamethasone	23 (11.5)	0.65 (0.41–1.04)	(0.37–1.15)
Epinephrine	29 (14.6)	0.79 (0.51–1.23)	(0.47–1.34)
Dexamethasone	31 (15.5)	0.85 (0.56–1.31)	(0.51–1.43)
By day 7			
Placebo	53 (26.4)	1.00	
Epinephrine and dexamethasone	34 (17.1)	0.65 (0.45–0.95)	(0.41–1.03)
Epinephrine	47 (23.7)	0.88 (0.63–1.23)	(0.59–1.32)
Dexamethasone	51 (25.6)	0.96 (0.69–1.33)	(0.65–1.42)
By day 22			
Placebo	54 (26.9)	1.00	
Epinephrine and dexamethasone	37 (18.5)	0.69 (0.48–0.99)	(0.44–1.07)
Epinephrine	50 (25.1)	0.92 (0.66–1.27)	(0.62–1.36)
Dexamethasone	53 (26.5)	0.98 (0.71–1.35)	(0.66–1.44)

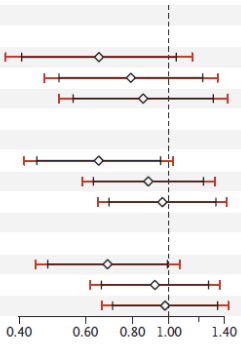


Figure 2. Frequency and Relative Risk of Hospital Admission on the Day of the Initial Emergency Department Visit, by Day 7, and by Day 22.

The red horizontal lines represent the 95% confidence intervals (CIs) for the adjusted comparisons and the black horizontal lines represent the 95% CIs for the unadjusted comparisons. Values of less than 1.00 favor the intervention.

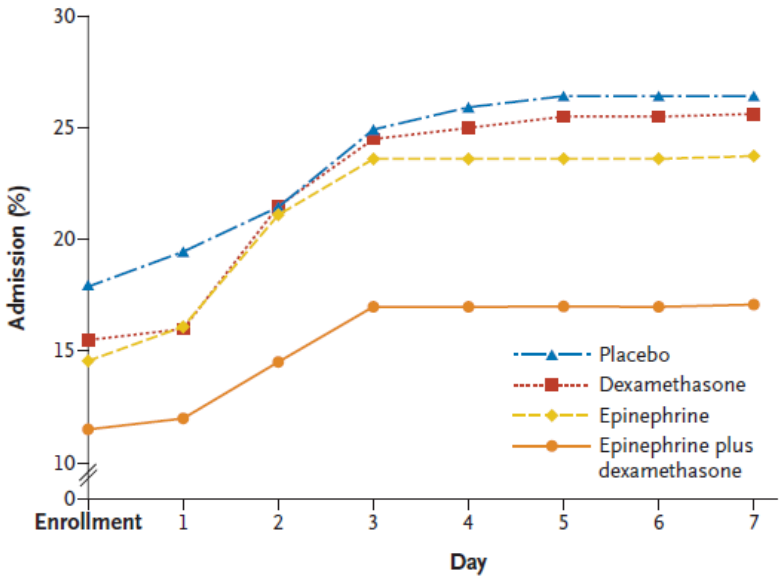


Figure 3. Cumulative Admissions during the First 7 Days after the Initial Emergency Department Visit, According to Study Group.

Enrollment data represent all patients admitted at their initial visit to the emergency department, and data for day 1 represent patients admitted within 24 hours of this visit.

The prelude to the DAB trial

- Minor adverse events
- 9.5% had palor
- 2% had tremor and vomiting
- There was no difference in adverse events between the groups
- Out of 800 patients only 1 admitted patient had mild transient hypertension

The prelude to the DAB study

- This marginally positive study opens this therapy for investigation in sicker patients
- Does this combination therapy impact the clinical course in those who require intensive care therapy?

Randomised controlled trial of a combination of Dexamethasone and Adrenaline for Bronchiolitis

- Randomised controlled trial
- RCH (Melbourne) Princess Margaret (Perth) Starship and Middlemore (Auckland)
- Starting in 2013 (hopefully March)
- Dexamethasone and adrenaline and standard care vs standard care alone in those admitted to intensive care with bronchiolitis

The DAB trial

- What is the research question?

- Does the combination of dexamethasone and nebulised adrenaline reduce the duration of positive pressure respiratory support (HFNPO2, NIV, MV) in children admitted to the ICU with Bronchiolitis.

The DAB trial

- **Inclusion criteria**
- a clinical diagnosis of bronchiolitis, defined as a first or second episode of wheezing or respiratory distress associated with a respiratory tract infection plus either radiological evidence of chest hyperinflation or clinical evidence of prolonged expiration
- less than 18 months of age
- no previous admission to this study
- admission to intensive care for respiratory distress (not apnoea alone)
- recruitment and initiation of the study therapy within 4 hours of admission to intensive care (including PETS)

The DAB trial

- **Exclusion criteria**
- Corrected gestational age of less than 37 weeks at time of admission to the intensive care.
- Clinical evidence of croup (laryngotracheobronchitis)
- Immunosuppressive treatment, including any dose of corticosteroids in the last 7 days.
- Apnoea without respiratory distress

Randomisation

- On line randomisation
- Unblinded study ie all are aware of the allocation
- Intervention – standard care and steroids/adrenaline
- Control group – standard care ie what we normally do for bronchiolitis
- Subgroups to be analysed – CLD, cyanotic heart disease,

The DAB trial

- **Intervention**
- Dexamethasone 0.6mg/k followed by IV methylprednisolone 1mg/k 8/24 or oral/NG prednisolone 1mg/kg 8/24 for 9 doses (3 days)
- Daily steroid therapy 1mg/kg for a further 3 days
- Adrenaline nebs – 5 doses given half hourly at the commencement of dexamethasone then 1-4 hourly prn for 3 days then prn for the following 3 days
- Standard care – nutrition, supportive care

The DAB trial

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
dexamethasone	once					
Methylpred/pred	8/24	8/24	8/24	d	d	d
Adrenaline	1-4/24prn	1-4/24prn	1-4/24prn	prn	prn	prn
Adrenaline *	5 doses half hourly					

- On admission with IV or IM dexamethasone
- Trial stops for each patient at ICU discharge

Outcomes

- Primary outcome

Duration of non-invasive or invasive positive pressure support required from the time of admission to the study until discharge from intensive care

Outcomes

- The secondary outcomes

1. Duration of mechanical ventilation
2. Length of stay (ICU)
3. Length of stay (Hosp)
4. Intubation
5. Pressure Rate product if NGT already in situ

Practicalities

- Identifying a subject
- ED
  - Any prior duration in ED but must be randomised within 4 hours of ICU admission
  - Can start process if patient is waiting for an ICU bed
- PETS
  - If child is going to be retrieved by PETS and admitted to PICU randomisation can take place at referring hospital by PETS registrar.
  - NETS TBA
- Ward
  - Any ward duration prior to ICU admission
  - Remember not eligible if recent steroid prescription

Practicalities

- What to do when identified
- Roster for recruitment Ben Siva or Frank
- Other senior reg or consultant not looking after the patient can help with recruitment
- After hours it can be the clinician caring for the child
- Resource folder
- Must record all recruited AND non recruited in the **DAB study book** attached to the study folder
- On line randomisation – being arranged through website coordinated from Auckland
- Drug charts
- Trial work sheets (case report forms CRFs)
- Adverse event reporting
- Once discharged

Resource folder

- Where it lives
- Protocol
- Consent forms
  - Once signed place in resource folder
- How-to-guide for randomisation (still to come)
- Example drug chart
- Stickers for drug charts
- Subject Case Report Form

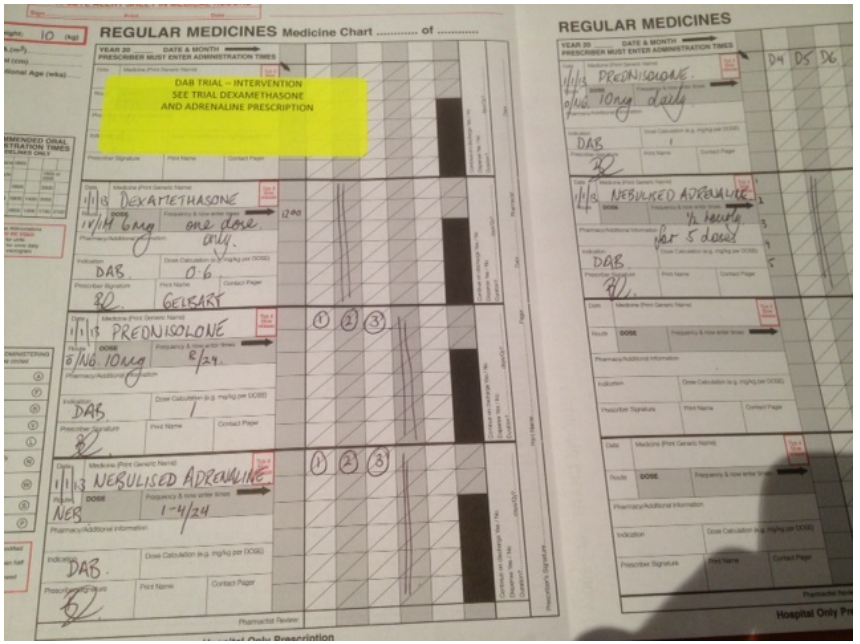
- Picture of resource folder – still being developed

On-line randomisation

- Website being developed by New Zealand site
- Enter patient study number and treatment group in the **DAB Study Book (near resource folder)**
- Picture of

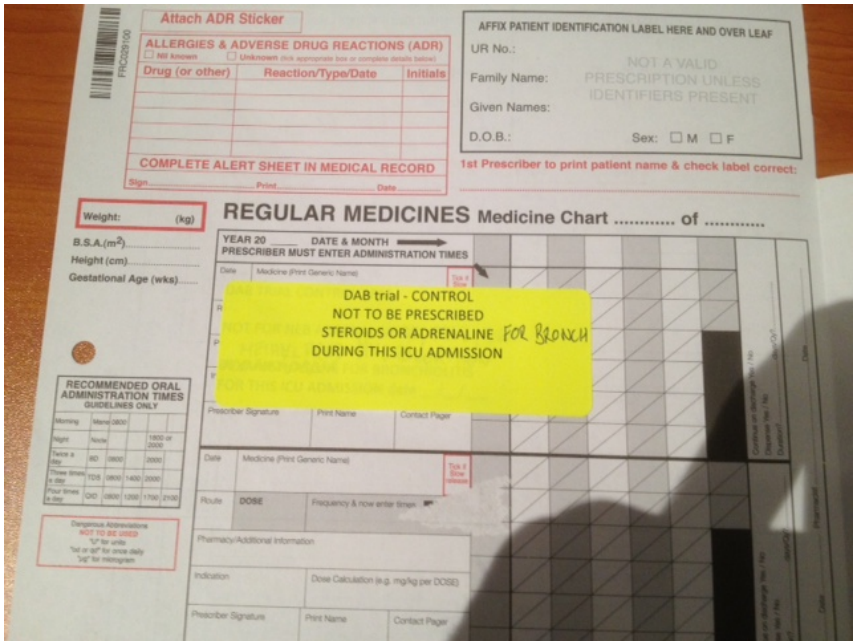
On-line randomisation

- If randomised to intervention
- Sign to be placed at bedside
- Drug chart prescribed as indicated in the resource folder
- Sticker placed indicating that dexamethasone and adrenaline are study drugs and are not to be ceased until discharge



On-line randomisation

- If randomised to control
- Sign to be placed at bedside
- Sticker DAB trial not for steroids or nebulised adrenaline to be placed in the drug charts



Study design

- Once randomised
- Study book entry
- Prescription of medications
- CRF
  - To be filled out by Ben, Frank Siva, Carmel
- Support – Ben Siva Carmel and Frank will be available by phone for assistance

The DAB trial

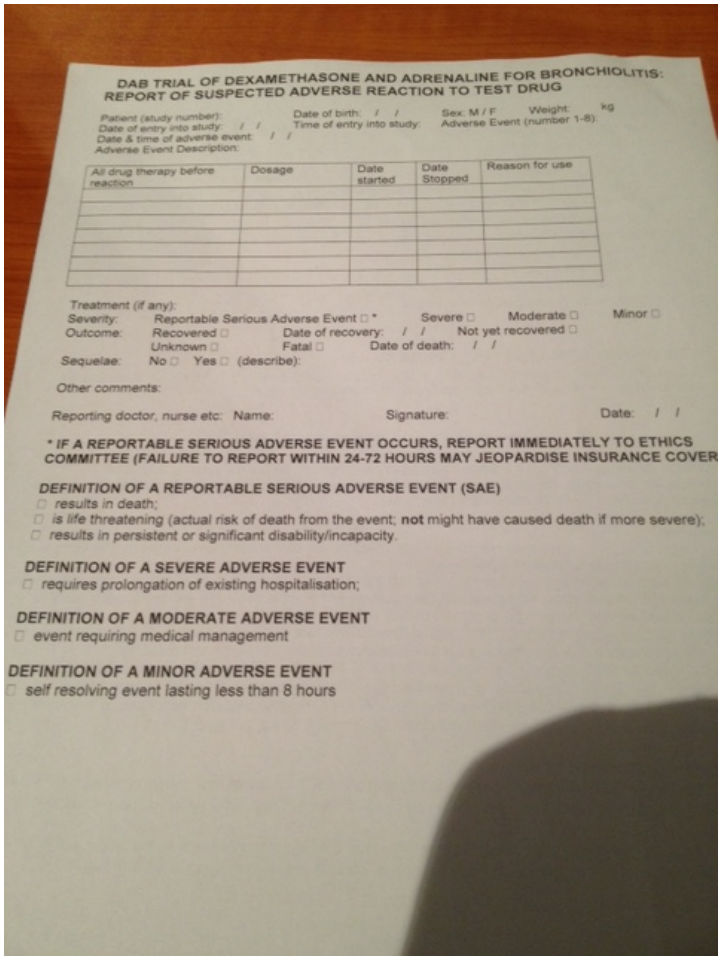
- Aim to recruit 306 patients total from all sites
- Likely to take 3-4 seasons
- Interim assessments of the data by a Data Safety Monitoring Committee

Adverse events

- Arrhythmia
  - Minor
  - Atrial or ventricular
  - Severe (reportable)
- Hypertension
  - Severe - Persistant (greater than 30 mins) of 30% above upper limit of resting mean BP for age
- Pallor agitation

Adverse Events

- Adverse event reporting
- **Mild** – self resolving event
- **Moderate** – event requiring medical management
- **Severe** - requiring prolongation of existing hospitalisation
- **Reportable serious adverse event**
- See last page of patient work sheet (CRF)



DAB TRIAL OF DEXAMETHASONE AND ADRENALINE FOR BRONCHIOLITIS:
REPORT OF SUSPECTED ADVERSE REACTION TO TEST DRUG

Patient (study number): Date of birth: / / Sex: M / F Weight: kg
Date of entry into study: / / Time of entry into study: Adverse Event (number 1-8):
Date & time of adverse event: / /
Adverse Event Description:

All drug therapy before reaction	Dosage	Date started	Date Stopped	Reason for use

Treatment (if any):
Severity: Reportable Serious Adverse Event ☐ * Severe ☐ Moderate ☐ Minor ☐
Outcome: Recovered ☐ Date of recovery: / / Not yet recovered ☐
Unknown ☐ Fatal ☐ Date of death: / /
Sequelae: No ☐ Yes ☐ (describe):

Other comments:

Reporting doctor, nurse etc: Name: Signature: Date: / /

* IF A REPORTABLE SERIOUS ADVERSE EVENT OCCURS, REPORT IMMEDIATELY TO ETHICS COMMITTEE (FAILURE TO REPORT WITHIN 24-72 HOURS MAY JEOPARDISE INSURANCE COVER

DEFINITION OF A REPORTABLE SERIOUS ADVERSE EVENT (SAE)
☐ results in death;
☐ is life threatening (actual risk of death from the event; **not** might have caused death if more severe);
☐ results in persistent or significant disability/incapacity.

DEFINITION OF A SEVERE ADVERSE EVENT
☐ requires prolongation of existing hospitalisation;

DEFINITION OF A MODERATE ADVERSE EVENT
☐ event requiring medical management

DEFINITION OF A MINOR ADVERSE EVENT
☐ self resolving event lasting less than 8 hours

Adverse events

- Reportable serious adverse events - need to be reported to investigator immediately
- Need to be reported to ethics committee within 72 hours
- Definitions
  - Results in death
  - Life threatening
  - Results in persistent or significant disability

Thanks for supporting this important trial

- Questions???
- More details to follow on resources and randomisation

Risk factors for outcomes

Peidatrics125:2
Feb 2010

TABLE 1 Selected Risk Factors for Outcomes of Bronchiolitis in 3 Prospective Studies of Outpatients

	Shaw et al[38] (1991)	Mansbach et al[40] (2008)	Voets et al[39] (2006)
Outcome	Severe disease[a]	Hospitalization	Hospitalization
Risk factors			
Age			
<2 mo		4.5/0.78	
<3 mo	2.2/0.75		
<6 mo			2.2/0.53
Prematurity			
<34 wk	5.4/0.77		
<35 wk		1.5/0.96	
Ill appearance	3.2/0.32		
Oxygen saturation			
<94%		5.4/0.77	
<95%	16/0.69		5.2/0.37
Respiratory rate			
>45 breaths per min			3.8/0.39
At or higher than normal for age (40–45 breaths per min according to age)		1.3/0.61	
≥70 breaths per min	5.8/0.75		
Work of breathing			
Accessory muscle use	2.2/0.42		
Moderate/severe retractions		3.2/0.76	
Chest radiograph result			
Atelectasis	10.5/0.81		
Abnormal		1.2/0.73	

Risk factors are presented as positive or negative likelihood ratios (+LR/−LR). The likelihood ratio can be multiplied by the pretest odds (ratio of the risk/1-risk) to obtain the posttest odds. For example, with a previous risk of hospitalization of 33% (odds of 0.33/0.66 = 0.5), a finding with a positive likelihood ratio of 4 increases the odds to 2 (4 × 0.5), corresponding to a posttest risk of 67% (2/2 + 1).

[a] Severe disease was defined as unable to maintain alert, active, and well hydrated while taking oral fluids throughout the illness.

Adapted with permission from Zorc JJ. *Recent Advances in Paediatrics*. London, United Kingdom: Royal Society of Medicine Press; 2009:19.

Dexamethasone in ventilated infants with RSV?

- 12 ICUs UK Netherlands
- Children less than 2 MV with RSV
- Placebo controlled
- Dex 0.6mg/k/d 6 hourly
- Primary outcome duration of mechanical ventilation
- Mild PF>200 PEEP <10
- Severe <200 PEEP >10
- Slow to recruit and no difference between groups

Table 2. Primary and secondary outcome measures univariate analysis

Mild Oxygenation Abnormalities Subgroup	Dexamethasone (n = 45) Median (IQR)	Placebo (n = 44) Median (IQR)	p^a
Duration of mechanical ventilation, hrs	137 (91–195)	139 (117–188)	.60
Length of stay in the pediatric intensive care unit, hrs	168 (120–252)	192 (168–264)	.22
Length of stay in the hospital, hrs	300 (250–396)	300 (216–432)	.80
Duration of supplemental oxygen, hrs	240 (144–276)	240 (168–288)	.58
Severe Oxygenation Abnormalities Subgroup	**Dexamethasone (n = 28) Median (IQR)**	**Placebo (n = 28) Median (IQR)**	p^a
Duration of mechanical ventilation, hrs	171 (136–212)	170 (125–201)	.60
Length of stay in the pediatric intensive care unit, hrs	192 (156–228)	192 (144–216)	.84
Length of stay in the hospital, hrs	408 (324–564)	360 (300–408)	.09
Duration of supplemental oxygen, hrs	216 (192–312)	240 (216–336)	.69

IQR, interquartile range.
[a]Mann-Whitney *U* test.

Crit Care Med 2011 Vol. 39, No. 7

Dexamethasone for RSV LRTI

Thorax 2003;**58**:383–387

Table 1 Characteristics of patients on admission in the PICU according to treatment group

	Dexamethasone (n=37)	Placebo (n=45)	p value
Male	30	27	0.054
Age (weeks)	5.9 (0.9)	9.8 (1.6)	0.04
Risk group	12	17	0.65
Premature*	10	12	1.0
CLD	1	2	1.0
CHD	1	1	1.0
Other†	0	2	0.5
Family history of asthma‡	9	11	1.0
Duration of symptoms (days)	3.3 (0.3)	3.6 (0.3)	1.0
Apnoea	5	9	0.55
Wheezing	16	21	0.83
Admission weight (kg)	4.1 (0.2)	4.3 (0.2)	0.32
Median (IQR) PRISM score	9 (7–12)	10 (7–12)	0.97
SIMV/PC	28	29	0.34
Median (IQR) PIP (cm H_2O)§	24 (20–26)	24 (22–26)	0.72
Median (IQR) PEEP (cm H_2O)§	4 (4–5)	4 (4–5)	0.70
Pa_{O_2}/Fi_{O_2} ratio (mm Hg)	180 (9)	173 (11)	0.77
Time elapsed between start mechanical ventilation and start trial medication (h)	15 (1.2)	14 (1.3)	0.53

CLD=chronic lung disease; CHD=congenital heart disease; SIMV/PC=synchronised intermittent mandatory ventilation, pressure controlled; PIP=positive inspiratory pressure; PEEP=positive end expiratory pressure.
*Prematurity was defined as a gestational duration of less than 36 weeks.
†One patient with cardiomyopathy, one patient with lung hypoplasia.
‡Mother, father or sibling with asthma.
§Only in patients with SIMV/PC ventilation.

Dexamethasone for RSV LRTI

Table 2 Mean (SE) duration of mechanical ventilation, length of stay (LOS) in the paediatric intensive care unit (PICU) and hospital, and duration of supplemental oxygen in the two treatment groups

	Dexamethasone (n=37)	Placebo (n=45)	95% CI for difference	p value
Duration of mechanical ventilation (days)	6.9 (0.7)	8.5 (0.9)	−3.8 to 0.8	0.19
LOS in PICU (days)	9.1 (0.9)	9.9 (0.9)	−3.4 to 1.8	0.53
LOS in hospital (days)	15.9 (1.5)	14.9 (1.2)	−2.8 to 4.7	0.52
Duration of supplemental oxygen (days)	10.0 (1.2)	10.9 (1.0)	−3.9 to 2.1	0.55

Table 3 Mean (SE) duration of mechanical ventilation, length of stay (LOS) in the paediatric intensive care unit (PICU) and hospital, and supplemental oxygen in days in the two treatment groups according to subgroup analysis*

	Dexamethasone	Placebo	95% CI for difference	p value
Bronchiolitis group†				
n	18	21		
Duration of mechanical ventilation	4.9 (0.5)	9.2 (1.6)	−7.8 to −0.8	0.02
LOS PICU	7.9 (1.4)	10.3 (1.6)	−6.8 to 2.0	0.28
LOS hospital	14.9 (2.0)	16.0 (1.9)	−6.7 to 4.5	0.11
Duration of supplemental oxygen	7.7 (0.9)	11.3 (1.6)	−8.0 to −0.1	0.048
Pneumonia group‡				
n	19	22		
Duration of mechanical ventilation	8.9 (1.1)	8.1 (1.0)	−2.2 to 3.6	0.61
LOS PICU	10.1 (1.1)	9.9 (1.2)	−3.1 to 3.5	0.90
LOS hospital	16.7 (2.2)	14.1 (1.5)	−2.8 to 8.0	0.34
Duration of supplemental oxygen	12.1 (1.9)	10.4 (1.0)	−2.7 to 6.1	0.50

*Arterial blood gas analysis was available for 37 patients in the dexamethasone group and 43 patients in the placebo group.
†Bronchiolitis group: patients with PaO_2/FiO_2 >200 mm Hg and/or mean airway pressure ≤10 cm H_2O.
‡Pneumonia group: patients with PaO_2/FiO_2 ≤200 mm Hg and MAP >10 cm H_2O.

Dexamethasone and effect on RSV induced lung inflammation

- Does dexamethasone alter the RSV induced cytokine and chemokine response?
- Texas group – 1997-8 and 1998-9
- Data from RCT of dexamethasone v placebo for intubated children with RSV
- Tracheal aspirates on D0 D1 D5
- Cytokines – interleukins TNF
- Chemokines – macrophage inflammatory protein, interferon inducible protein
- Lab and clinical markers - RSV cultures LOMV LOS

Dexamethasone and effect on RSV induced lung inflammation

- No correlation between dexamethasone and cytokine expression or clinical course
- Therefore the group concludes
- corticosteroids dont work in bronchiolitis!
- It only delays the clearance of RSV as documented in the origincal RCT

Table 2. Cytokine concentrations in tracheal aspirates

	Day 0			Day 1			Day 5		
Cytokines (pg/ml)	Placebo N = 19 Median (25th–75th)	Dexamethasone Median (25th–75th)	p-value	Placebo N = 19 Median (25th–75th)	Dexamethasone N = 22 Median (25th–75th)	p-value	Placebo N = 11 Median (25th–75th)	Dexamethasone N = 10 Median (25th–75th)	p-value
IL-1	266.5 (132.6–353.4)	230.6 (139.0–471.2)	0.7	189.4 (114.5–348.2)	217.6 (75.7–286.1)	0.38	264.7 (82.7–328.5)	293.9 (87.2–483.3)	0.53
IL-2	11.3 (5.9–17.1)	16.5 (5.3–26.5)	0.26	19.4 (8.3–40.1)	27.1 (8.6–42.3)	0.75	17 (13.3–37.4)	23.6 (3.2–45.7)	0.92
IL-1R	7616.5 (2748–21673)	7616.5 (3216–1587.7)	0.84	11286.4 (7200–14039)	10398.8 (5409–18900)	1	5321.2 (3235–7389)	12410 (5368–19614)	0.06
IL-2R	436.5 (363–608)	456.3 (340–605)	0.67	501.1 (393–527)	484.5 (289–629.4)	0.6	387.8 (363–500)	454.3 (336–556.4)	0.77
IL-4	5 (5–5)	5 (5–5)	1	38 (5–38.5)	37.1 (5–39.2)	0.89	37.4 (37.0–37.7)	21.3 (5–38)	0.39
IL-6	724 (294.7–1270.3)	752.2 (239.3–1207.1)	0.94	**419.9 (347.5–718.7)**	**212.5 (86.1–480.1)**	**0.006**	184.6 (50.5–433.4)	470.4 (136.4–745.7)	0.13
IL-7	167.1 (161.8–174.3)	169.1 (169.0–176.1)	0.76	90.1 (82.8–159.8)	91.1 (84.3–150.1)	0.74	**77.8 (77.4–89.3)**	**125.1 (88.6–164.2)**	**0.01**
IL-8	11842 (6790.0–24592)	14270 (5547–23587)	0.86	6647 (3694.2–10990.5)	4582 (2577–9224)	0.17	**2456.5 (704.2–6889.7)**	**10511 (4786–24482)**	**0.03**
IL-10	132.4 (106.8–151.1)	146.6 (113.8–169.9)	0.24	111.7 (101.5–139.0)	119.8 (108–143.5)	0.33	95.7 (76.7–106.7)	107.9 (95.8–143.5)	0.09
IL-12	409.2 (209.8–678.4)	659.5 (326.2–945.6)	0.17	151.8 (91–473.2)	111.4 (71.5–471.05)	0.22	41.4 (10.2–66.5)	79.7 (21.5–92.9)	0.43
IL-13	**31.2 (30.67–31.22)**	**31.22 (31.22–31.78)**	**0.003**	31.2 (30.6–31.7)	31.2 (30.6–59.6)	0.49	**7.3 (7.3–51.2)**	**35.5 (30.9–60.2)**	**0.01**
IL-15	**33.96 (31.92–37.04)**	**37.04 (33.96–43.28)**	**0.02**	82.8 (33.3–102.7)	75.7 (33.1–132.4)	0.8	52.5 (40.0–60.1)	58 (35.5–93.5)	0.61
IL-17	64.3 (57.2–69.9)	63 (57.2–72.1)	0.97	54.6 (10.2–60.6)	58.4 (20.3–63.0)	0.35	10.9 (10.2–59.0)	62 (43.4–66.6)	0.07
IP-10	589.6 (141.1–905.1)	156.8 (21.9–1218.5)	0.81	360.5 (202.2–1568.4)	162.9 (24.3–1228.8)	0.07	99.6 (11.0–134.5)	14.6 (12.6–76.5)	0.94
MIG	137.5 (84.0–569.1)	203.3 (93.7–455.2)	0.54	136.7 (102.6–226.9)	108.5 (84.8–168.0)	0.2	92.5 (82.8–137.7)	110.2 (79–194.3)	0.39
MIP-1α	282.6 (142.5–571.8)	207.5 (136.9–744.5)	0.81	177.4 (132.5–314.5)	103.7 (87.2–220.0)	0.12	**82.2 (44.9–90.5)**	**187 (81.5–680.0)**	**0.03**
MIP-1β	661 (118.8–1812.4)	681.3 (202.5–1752.5)	0.68	715.1 (314.8–850.2)	443.5 (240.9–949.5)	0.23	325.5 (161.7–389.0)	456.8 (89.5–1750.0)	0.29
RANTES	76.1 (52.9–153.1)	73.2 (49.3–128.1)	0.64	62.4 (49.3–82.9)	59.4 (42.7–90.4)	0.81	40.8 (16.4–80.3)	64.8 (42.4–81.3)	0.35
TNF-α	10 (10–53.6)	17 (10–78.1)	0.47	59.3 (30–79.7)	55.1 (10–205.2)	0.96	24.6 (10.2–67.6)	31.4 (10–484.4)	0.9
IFN-α	115.8 (106.7–127.0)	115.8 (106–134.9)	0.7	241.6 (119.2–338.9)	230.4 (120.9–309.9)	0.77	253.4 (192.9–324.1)	153 (105.4–230.4)	0.82
IFN-γ	14.1 (10.8–18.4)	22.2 (11.4–35.9)	0.3	16.3 (2.90–23.9)	13.3 (5.8–25.8)	0.88	2.9 (2.9–20.8)	13.5 (5.0–21.4)	0.07
MCP-1	2965 (815.1–5770.4)	5082 (2463.9–7634.9)	0.14	**1626.2 (895.5–3472.8)**	**516.9 161.1–955.3)**	**0.001**	470.9 (271.4–810.6)	546.7 (188.9–1010.4)	0.84
Eotaxin	16.9 (8.4–32.4)	6.3 (5–11.7)	0.12	**8.4 (5–13.1)**	**5.2 (4.8–8.2)**	**0.02**	5 (5–8.0)	5.1 (4.7–6.6)	0.84
GM-CSF	65.5 (64.9–67.0)	64 (61.1–69.8)	0.15	64 (35.5–66.2)	203.9 (67–224.4)	0.78	43.6 (26.1–63.3)	64 (61.1–214.2)	0.1

Tracheal aspirates from 41 infants intubated with RSV bronchiolitis were collected on days 0, 1 and 5 and measured for cytokine concentrations with a multiplex bead assay. Values are expressed as medians (25–75% percentiles). IL-5 was below the limit of detection at all time points. The cytokine lower limits of detection were: IL-1 (15 pg/ml), IL-2 (6 pg/ml), IL-1R (30 pg/ml), IL-2R (30 pg/ml), IL-4 (5 pg/ml), IL-6 (3 pg/ml), IL-6 (3 pg/ml), IL-7 (10 pg/ml), IL-8 (3 pg/ml), IL-10 (5 pg/ml), IL-12p40 (15 pg/ml), IL-13 (7 pg/ml), IL-15 (10 pg/ml), IL-17 (10 pg/ml), TNF-α (10 pg/ml), IFN-γ (5 pg/ml), IFN-γ (15 pg/ml), GM-CSF (15 pg/ml), MIP-1α (10 pg/ml), MIP-1β (10 pg/ml), IP-10 (5 pg/ml), MIG (4 pg/ml), eotaxin (4 pg/ml), RANTES (15 pg/ml) and MCP-1 (10 pg/ml). Statistically significant ($p < 0.05$) results are presented in bold font.

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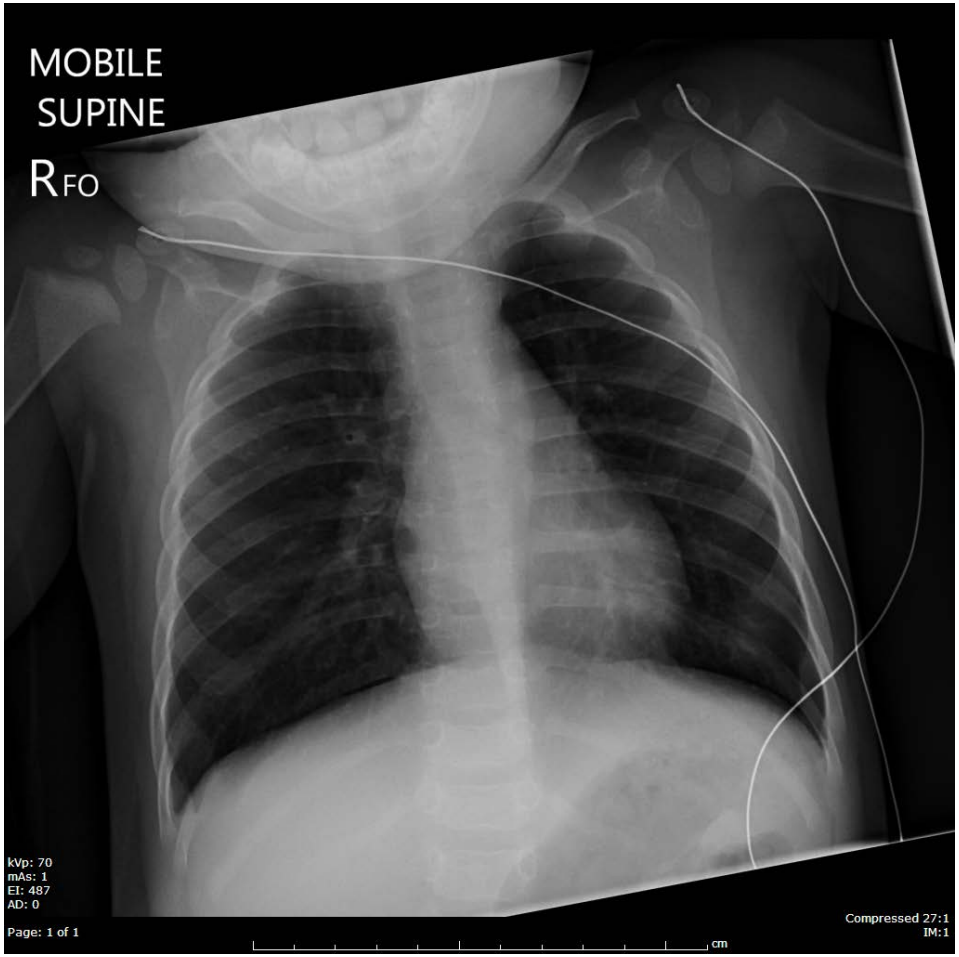
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