PARIS – Study Specifics

High Flow Nasal Cannula therapy in infants with bronchiolitis, a randomised controlled trial
PARIS (Paediatric Acute Respiratory Intervention Studies)

PREDICT and PCCRG NHMRC sponsored Study

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PARIS Discussion points

- Ethics
- Governance
- Adverse events
- Pilot Trial -> Multicentre International RCT
- Practical logistic set ups of 17 centres
- Educational components
- Database & Data collection
- Papers
PARIS Ethics

• NEAF
• Children’s Health Qld HREC (Pilot/larger RCT)
• Individual hospital HREC/HDEC
  – NZ HDEC in person (delayed consent)
• Amendments throughout RCT
PARIS Ethics

• Amendments (CHQ and locally)
  – Adding additional sites
  – Parent Flyer
  – Delayed Consent rules surrounding date collection
  – Delayed Consent use of telephone consents
  – Feeding question

• Serious Adverse Events
  – Prompt reporting DSMB and Ethics
PARIS Governance

17 centres with varied processes
  * 4 Australian States  * 2 countries

Requirements each centre:

1. **Site Specific Application** (SSA) (include in-kind costs)
   – provide relevant docs (HREC’s, CRF’s, Consents, Protocol – track changed for specific hospital)

2. **Clinical Trials Research Agreement** (CTRA) – individual centres (DoV – Schedule 2)

3. **Public Health Act** (PHA) + Victorian Specific Module
   (equipment & consented/non-consented patients)
PARIS Governance Challenges

• Qld – varied with same overarching guideline for 11 centres (SSA requirements)
• SSA – Section 18 (Funding) clarity
• CTRA (Medicines Australia template) – some centres very specific about equipment/consumables
• Advantageous for same consistent team with CTRA and MIA (funding details)
• PHA for Qld – timeframe with Director-General
Governance with NHMRC funding

Multi-institutional agreement (MIA)
• Is a multiparty collaborative agreement
• Governs conduct of the grant and disbursement of grant funds to CI sites
• NHMRC CI centres receive additional secondary gain as NHMRC institution behind it.
• CTRA (funding) – for non MIA parties (other PI’s)

Lessons learned
• Get started early! (Legal sign off locally) Four sites for PARIS
PARIS Serious Adverse events

• Timely manner (within 24-72hrs) to:
  – Report to DSMB (2 independent members)
  – Report to governance/HREC (local & central - CHQ HREC)
  – Feedback to relevant team involved
  – Action changes required if outlined
Serious Adverse Event

PI report to local governance/HREC & Study CI-> detailed report (duration of treatment and outcome)

PI implement changes if applicable

CI report to PI outcome and changes/advice

HREC reply with letter of advice to CI

CI report to HREC details, outcome and DSMB changes/advice

DSMB review

DSMB request further information

DSMB feedback to CI with changes/advice for trial

CI report to DSMB detailed report

DSMB review

CI report to PI outcome and changes/advice
PARIS Serious Adverse Events

• 2 serious adverse events reported to date (July and Oct 2015) – pneumothorax – Control & High Flow

• Reporting – one prompt and one late as central team picked up

Event 1 description

Event 2 description

Lessons learned with late reporting -

• Failed to educate local team to report in a timely manner.
Supposed adverse event -> improved study outcome

- Suspension of Trial 5 days in Qld affecting 5 centres
- Inaccurate reporting to the Patient Safety Unit (PSU)
- 5 days to clarify with QH/CHQ Exec
- Good outcome as improved reporting from PSU and improved EWT’s
Pilot Trial -> Multicentre International RCT

• Pilot trial essential – included elements of final trial to test intervention
• Iron out problems
• Commenced with one centre (Nov 2013 start)
• NHMRC funded -> 17 centres within 10 months
• Lessons learned from pilot trial
  – Revised Protocol – treatment failure (40% FiO2)
  – Champion Booklet
  – Key leaders established (nursing in regional centres)
  – Improved documentation
Practical logistic set ups of centres – differences

• Randomisation from ED and ward in some centres
• ED not involved in one centre
• Site visits VITAL – establish understanding of baseline (staff, EWT’s, pt flow, use of HF and current guideline/where used, mixed ED’s and paediatric training, ICU on-site)
• SSU – include or not include (effects screening log data).
Educational resources PARIS

- Face to face nursing and medical education – with/without presentations (voiceover)
- Educational package for PREDICT centre Research Nurses
- Locally funded RA’s
- Refresher presentations
- Patient Booklet – step-by-step guide
- Champion Booklets
- Early Warning Tools (EWT) x 9 versions (ED & Ward)
- Signage – Champions names & badges/flowcharts
- Lanyards
- Troubleshooting Guide
- FAQ’s
- Airvo2 app and signage
Educational resources
PARIS
Patient Booklet

PAEDIATRIC BRONCHIOLITIS MANAGEMENT
PATIENT BOOKLET

PATIENT BOOKLET
High Flow Nasal Cannula (HFNC) Treatment Management for Viral Bronchiolitis

Parent Information Flyer
Educational resources
PARIS
Champion Booklet

CHAMPION’S RESOURCE PACKAGE
High Flow Nasal Cannula (HFNC) Treatment
Management for Viral Bronchiolitis - RCT
Educational resources

PARIS

EWT’s

9 versions of CONTROL
9 versions of HIGH FLOW
9 versions of ESCALATION
Educational resources
PARIS
Signage
9 VERSIONS

**EDUCATIONAL RESOURCES**

**PARIS**

**FLOWCHARTS**

**STUDY PROTOCOL SCREENING**

**Diagnosis Bronchiolitis and < 1yr corrected age**

- **Eligibility? Baseline observations - does the infant NEED Oxygen?**
  - **YES**
    - **Bronchiolitis with Oxygen requirement**
    - **ENTER STUDY**
      - Go to study box for randomisation and CHOOSE ENVELOPE in sequential order
      - **CONTROL**
        - Current hospital management
      - **HIGH FLOW (HFNC)** Treatment
    - **NO Oxygen requirement**
      - **Admitted to hospital**

- **NO**

**EXCLUSION CRITERIA**
- Upper airway obstruction
- Apnoea
- Craniofacial malformation
- Critically ill: urgent need for NIV or intubation and ventilation and/or decreased consciousness
- Basal skull fracture
- Trauma
- Cyanotic Heart Disease
- Home oxygen therapy

**INCLUSION CRITERIA**
- < 12 months corrected age
- SpO2 < 94% in room air
- If Oxygen given in ambulance, turn off and test SpO2 in ED

**Delayed Consent** in ward by Paediatrician, Registrar or Nurse
CONTROL GROUP
Current hospital management

Recheck SpO2

If SpO2 < 94% give Oxygen
(0-2L/min as per current hospital protocol)
Target SpO2 range 94-98%

If SpO2 ≥94% wean Oxygen

If SpO2 <94% increase Oxygen

RESPONDERS to Control Treatment are identified by the following:
- HR decreasing by 15 bpm since admission AND
- RR decreasing by 5-6 resps/min since admission AND
- CEWT score ≤5 range AND
- Oxygen requirement is less than 2L/min to maintain SpO2 ≥94%

NON-RESPONDERS to Control Treatment are identified only if the infant displays THREE of the FOUR following clinical parameters. Consider escalation to HIGH FLOW TREATMENT (HF) arm if THREE criteria are met:
- HR remains unchanged or increases since admission
- RR remains unchanged or increases since admission
- CEWT score within 6-7 range
- Oxygen requirement is > 2 L/min to maintain SpO2 ≥94%

Please follow the study protocol closely, and allow at least 3 hrs or more of observations prior to escalation of treatment. However, if you are concerned that your patient is deteriorating rapidly at any stage, then it is acceptable to take the necessary steps such as escalation/intubation and referral to GCUH or Tertiary ICU bed.

HIGH FLOW (HF) With FiO2 2 Treatment
HIGH FLOW (HFNC) Treatment
2L/kg/min (max. 25L/min)

<85%

Recheck SpO2

85-93%

High Flow WITH FiO2

High Flow in ROOM AIR (FiO2=21%)

Observe SpO2 for 10 mins - if still <94% increase FiO2 and titrate accordingly

Maintain SpO2 94-98% titrate FiO2 accordingly

Non-Responders to High Flow with FiO2 arm may consider escalation of care and TRANSFER to GCUH-CCU if THREE of the FOUR following clinical parameters are met.

- HR remains unchanged or has increased since admission
- RR remains unchanged or has increased since admission
- CEWT score is within 6-7 range
- FiO2 required is >40% to maintain SpO2 >94%

Medical Officer to consider current resources (i.e. nursing) and use clinical judgment with review.

Responders to High Flow with or without FiO2

If SpO2 ≥94% reduce and wean FiO2

IF patient in room air (FiO2=21%) and SpO2 ≥94% for >4 hrs cease High Flow

See Weaning Flow Chart

Contact GCUH Children’s ICU Specialist/Registrar or RSQ (1300 799 127) for transfer

Please follow the study protocol closely, and allow at least 3 hrs or more of observations prior to escalation of treatment. However, if you are concerned that your patient is deteriorating rapidly at any stage, then it is acceptable to take the necessary steps such as escalation/intubation/referral.

Educational resources
PARIS
Flowcharts
TITRATING AND WEANING patients on HIGH FLOW with FiO2

Responders to High Flow with FiO2

WEANING FiO2
If SpO2 ≥94% wean and reduce FiO2 in 5% steps at regular intervals

Monitor for 10 mins in Room Air and if SpO2 remains <94% increase FiO2 to maintain SpO2 94-98%

If patient SpO2 <94% at anytime whilst monitoring and continuing observations, recommence High Flow at 2L/kg/min in Room Air (FiO2~21%)

If patient maintaining SpO2 94-98% or more for >4hrs on High Flow in Room Air (FiO2~21%)

Cease High Flow and remove nasal prongs and allow patient to breathe room air with no High Flow
Control Therapy
(Standard Oxygen Therapy)

- Document patients room air baseline vitals on hospital early warning tool chart
- If SpO2 <92% give Oxygen
- Apply standard hospital nasal prongs
- Give 0-2L/min as per current hospital protocol
- Aim for SpO2 92-98%
- If SpO2 stable and ≥92% wean Oxygen

High Flow Treatment
(HFNC)

Document patients room air baseline vitals on hospital early warning tool chart
Collect equipment
- AIRVO2, Circuit, Green Optiflow Nasal Cannula, water bag
- Turn AIRVO2 on and ensure paediatric mode (bird and butterfly on screen)
- Attach circuit and water bag
- Apply green optiflow nasal prongs
- Set HFNC flow at 2L/kg/min at all times (Max 25L/min for >12.5 kg)
- If SpO2 85-91% give HFNC in room air (FiO2=21%) for 10 mins
- If SpO2 <85% give HFNC with FiO2
- Aim for SpO2 92-98% and titrate FiO2 accordingly
- Refer to Weaning Flow Chart
<table>
<thead>
<tr>
<th>PROBLEM</th>
<th>SOLUTION</th>
</tr>
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| Incorrect L/minute on display screen for weight. | - Work out correct L/kg/minute for specific patient weight (e.g., 8 kg infant = 16 L/min of flow with AIRVO2)  
- Press the ‘MODE’ button (side arrow button) twice (as the first press will give you humidification and the second press will give you L/minute).  
- Press the up and down arrows together for 5 seconds to release the lock.  
- Then increase or decrease the L/minute displayed using up and down arrows.  
- Once reached correct L/minute, press the ‘MODE’ button again once for 1 second to lock. |
| Unable to increase Oxygen | - Check correct position of nasal prongs to ensure no occlusion exists, which includes secretions and/or positioning at nares.  
- Oxygen is manually increased using Oxygen flow meter at wall (needs to be a 15L/min flow meter).  
- Actual Oxygen being delivered to the patient is shown on the display screen (e.g., FIO2 of 30% may be 2 L/minute of flow at wall for a particular size of infant).  
- It’s important to observe the display screen FIO2 when increasing the Oxygen at the wall flow meter to achieve the FIO2 required to maintain SpO2. |
| Unable to decrease Oxygen | - Check correct position of nasal prongs to ensure no occlusion exists, which includes secretions and/or positioning at nares.  
- Decrease Oxygen at wall flow meter whilst observing the display screen FIO2.  
- With each small decrease on the wall you will see the FIO2 decrease on the display screen.  
- ROOM AIR = 21% FIO2  
- FIO2 Is Fraction of Inspired Oxygen |
| Machine alarming ‘Occlusion’ or ‘Blockage’ | - Check correct size of nasal prongs. Only green Optiflow nasal prongs for the High Flow study patients are to be used.  
- Check there are no kinks in the nasal cannula or the circuit.  
- Check that the display screen shows a bird and butterfly which represents ‘Junior Mode’ and if not, then AIRVO2 is in ‘Adult Mode’ and needs to be changed. To change to ‘Junior Mode’ hold the ‘Mode’ button (side arrow) down for 5 seconds until you see the bird and butterfly back on the screen. |
| Humidifier water level below maximum level (line allocated on chamber). | - Water is only required to cover the plate and does not have to reach the maximum line level allocated on the chamber.  
- There is a sensor floating ball in the chamber which prevents the humidifier from going dry (so long as there is a water bag with water in it). |
| Where does the AIRVO2 go once finished with its use? | - Return cleaned (wipe down with antibacterial wipes) and disinfected to INSERT DEPT/AREA. |
| Machine displays ‘Amber’ traffic light when switched on. Unsure if it can be used | - If ‘Amber’ traffic light is shown this means that the disinfection cycle has not been completed and needs to be done prior to using on a new patient.  
- A ‘Green’ traffic light indicates a disinfected and clean machine ready for new patient. |
| How to disinfect AIRVO2 after use with a patient? | - Remove all consumables using PPE from AIRVO2 and discard appropriately.  
- Attach red disinfection tubing (attached to the AIRVO2 pole) to machine.  
- Switch machine on  
- Machine will sense disinfection tubing and will automatically disinfect over a 55 minute period.  
- The display screen will show the time in minutes until completion. Once complete it will show a ‘tick’ symbol.  
- MUST switch machine off at on/off button prior to unplugging from wall. Otherwise it will alarm. |
4. How do I give a Nebulizer to a baby on High Flow with the AIRVO2 machine?

For the duration of the nebulizer, reduce the flow from the 2L/kg/min (ie if a baby is 10kg the baby will be on a flow of 20L/min) down to LOW FLOW at 2L/min. Do this by decreasing flow using AIRVO2 up and down arrows. Then increase the oxygen to 100% FiO2 by slowly increasing the flow to meet the required FiO2 on the machine screen.

5. What colour nasal prongs can I use on the paediatric circuit?

The Paediatric Circuit is suitable for two sizes of nasal cannulae on the AIRVO2, however for the purposes of the study, you will use mostly Green and on rare occasions with smaller infants, the Purple nasal cannulae. If you use purple nasal cannulae then please document on the early warning tool (observation chart) that you used the purple cannulae. Purple cannulae are used from the hospital stock present until it is noted that there is a large volume used and a need for these cannulae in this study and for this population of infants.

6. Do I use corrected age or chronologic age as 12 months?

Use only corrected age of infant when establishing if the patient meets inclusion criteria of less than 12 months of age. This means that if a baby is born at 32 weeks gestation (ie. 8 weeks earlier than planned/indicated), their corrected age is 8 weeks post their actual birthdate.

7. How many times can the same patient be enrolled in the study?

A patient can have one enrollment per admission - if they are on the trial and weaned off CONTROL or HIGH FLOW but require further therapy, be it CONTROL or HIGH FLOW, always document the last time they came off CONTROL or HIGH FLOW in the data form.

If the patient represents to the hospital again (and again) then they can be placed on the trial if they meet the inclusion criteria. New admissions require a new patient booklet and a new consent form to be completed.

8. If the infant is weaned off FiO2 and then weaned off High Flow and maintains SpO2 at 92% when awake but desaturates when asleep, do we return the infant to High Flow only when asleep?

The infant needs to go back on High Flow immediately as per weaning protocol. This means the infant is on High Flow at both sleep and awake times. The infant may only required a flow of 2L/kg/min in room air (FiO2 21%). Aim for saturations between 92-95% if maintained for >4hrs then turn High Flow off.

9. When High Flow is weaned and stopped, can we stop Nasogastric feeds and allow mum to breastfeed?

Yes.

10. When can I wean the infant’s FiO2 (High Flow patient) or standard wall Oxygen (Control patient)?

When the infants SpO2 is stable between 92-95% you can then wean the patient’s oxygen. You do not need to wait until the SpO2 are at 96% - you can start to wean when the SpO2 are stable and above 92%.

11. The baby has increased work of breathing however the saturations remain at 92%. Can I commence on High Flow for the work of breathing?

No, if you want to recruit this patient to the study. It is recognised that this is difficult for the medical and nursing staff to observe and not apply High Flow however this is the reason for the study taking place – to prove or disprove the effect and usefulness of High Flow against standard Oxygen therapy. The trial will have been working hard prior to presenting to the hospital while at home, and the infants will decline themselves by dropping their saturations at some point if this is going to occur. Admit the patient to the ward if you think this is what is needed and continue to observe and monitor SpO2.
Educational resources
PARIS
Airvo2 resources

• Smart phone APP
• Youtube link for set up
• Signage with Airvo2’s
Education Challenges PARIS

• Creep in effect -> HF already in use
• Flow rates adjustments initially
• Adherence to protocol
  WOB -> understanding Oxygen vs Flow
• Change of Dx to treat with HF
• Sometimes escalation criteria
• Oxygen toxicity
• NGT (mixed ED’s with more adult trained)
Educational benefits PARIS

• Standardised protocol (control or high flow)
Education
(Knowledge translation into practice)

• Collecting education numbers/times
• National Bronchiolitis Guidelines
• Statewide guidelines
• Measuring bronchiolitis management one year post PARIS I
• Grant submission
Educational future - High Flow

3 x Video Documentaries - mid 2016

- Physiology
- Current evidence and practice of HF in Emergency, General Paediatrics and ICU (guidelines in place)
- Process of implementation, research that has been influential
Database - WebSpirit

• Plan ahead well as cannot change database (can add but not remove)
• Layout is poor
• Costs involved – per site/per form
• Export cumbersome
• WebSpirit number vs Study ID
• Sites can review own data (Visit Status)
• FAQ for data entry users
PARIS Papers to be published

• Many ideas
• Main paper – outcomes analysis
• Physiology (EWT’s)
• Quality & Safety aspect (adverse events)
• Feeding
• Delayed Consent
CONSORT Statement
(Consolidated Standards of Reporting Trials)

• An evidence-based, minimum set of recommendations for reporting randomized trials.

• Standard way for authors to prepare reports of trial findings, facilitating their complete and transparent reporting, and aiding their critical appraisal and interpretation.

• **25-item checklist** - focus on reporting how the trial was designed, analysed, and interpreted

• **Flow diagram** - displays the progress of all participants through the trial.

• Endorsed by prominent general medical journals
CONSORT 2010 Flow Diagram

Enrollment

Assessed for eligibility (n= )

Excluded (n= )
- Not meeting inclusion criteria (n= )
- Declined to participate (n= )
- Other reasons (n= )

Randomized (n= )

Allocation

Allocated to intervention (n= )
- Received allocated intervention (n= )
- Did not receive allocated intervention (give reasons) (n= )

Follow-Up

Lost to follow-up (give reasons) (n= )
Discontinued intervention (give reasons) (n= )

Analysis

Analysed (n= )
- Excluded from analysis (give reasons) (n= )

Analysed (n= )
- Excluded from analysis (give reasons) (n= )
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