Local Guideline and Procedure

BRONCHIAL CHALLENGE TEST USING ARIDOL® (MANNITOL) FOR PAEDIATRIC PATIENTS AT JOHN HUNTER CHILDREN'S HOSPITAL

Sites where Local Guideline and Procedure applies	JHCH Paediatric Respiratory Laboratory
This Local Guideline and Procedure applies to:	
1. Adults	No
2. Children up to 16 years	Yes
3. Neonates – less than 29 days	No
Target audience	Clinical Respiratory Laboratory Staff
Description	Procedure and Guideline for Bronchial Challenge testing using Aridol® (Mannitol)

Go to Procedure

National Standards	NS 1, 2, 3, 4, 6, 8
Keywords	Aridol, Mannitol, children, bronchial challenge
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Related Legislation, Australian Standard, NSW Ministry of Health Policy Directive or Guideline, National Safety and Quality Health Service Standard (NSQHSS) and/or other, HNE Health Document, Professional Guideline, Code of Practice or Ethics:

- NSW Health Policy Directive _ Consent to medical and health care manual IB2020_010.pdf
- NSW Ministry of Health Policy PD 2013_043 Medication Handling in SW Public Health Facilities

Prerequisites (if required)	Respiratory Scientist/Hospital Scientist with Respiratory Lab experience.
Local Guideline and Procedure note	This document reflects what is currently regarded as safe and appropriate practice. The guideline section does not replace the need for the application of clinical judgment in respect to each individual patient but the procedure/s **require mandatory compliance**. If staff believe that the procedure/s should not apply in a particular clinical situation they must seek advice from their unit manager/delegate and document the variance in the patients' health record. If this document needs to be utilised in a Non Clinical Area please liaise with the Clinical Service to ensure the appropriateness of the information contained within the Guideline and Procedure.
Position responsible for and document authorised by	JHCH Clinical Quality Patient Care Committee
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PURPOSE AND RISKS

This local clinical guideline and procedure has been developed to provide instruction to the healthcare worker and to ensure that the risks of harm to the patient associated with the use of Aridol® (Mannitol) are identified and managed.

Bronchial provocation tests are used to elicit any hyper-responsiveness in the airway to a range of agents both specific and non-specific at varying strengths or quantities. Therefore, a dose response curve can be constructed.

If an airway shows hyper-responsiveness (a significant bronchospasm, defined as a significant fall in FEV1) to the challenge agent at a level of exposure deemed less than normal, then the clinician may use this information together with clinical information to determine whether this exaggerated broncho-constrictive response is asthma or not.

Since the end result and indeed the aim of the tests are to induce broncho-constriction, it implies inherent and mandatory safety precautions together with stringent exclusion criteria.

Airway hyper-responsiveness seems to be a composite physiological disorder of initial inflammation followed by constriction of the bronchi by the surrounding smooth muscle, the mechanisms of which have not clearly and fully been identified as yet but both genetic and environmental factors could be involved in its pathogenesis.

Inhalation challenge procedures also aim to try and measure the severity of any positive response, thus the methodology must be adhered to strictly, in order to achieve a reproducible uniform delivery of challenge substance from test to test and patient to patient.

Any unplanned event resulting in, or with the potential for, injury, damage or other loss to the patient as a result of this clinical procedure must be reported through the Incident Information Management System and managed in accordance with the Ministry of Health Policy Directive: Incident Management PD2007_061. This would include unintended patient injury or complication from treatment that results in disability, death or prolonged hospital stay and is caused by health care management.

Risk Category*: Clinical Care & Patient Safety*

GLOSSARY

Abbreviation/Word	Definition
FEV1	**Forced Expiratory Volume in 1 Second (the volume of air expired in the first second of a maximally forced exhalation)**
FVC	**Forced Vital Capacity (the maximum volume of air expired during a maximally forced exhalation)**
mg	**milligram**
mcg	**microgram**
bpm	**Beats per minute**
BHR	**Bronchial Hyper responsiveness**

GUIDELINE

This Guideline does not replace the need for the application of clinical judgment in respect to each individual patient.

The primary indication is to exclude (rule out) a diagnosis of asthma in those individuals with symptoms that suggest asthma (e.g. cough, wheezing or chest tightness following exposure to cold air, just after exercise, or during respiratory infections)

Other potential indications include: establishing a diagnosis of asthma, determining the relative risk of a healthy individual developing asthma, assessing the severity of asthma, assessing the response to therapeutic interventions and assessing occupational asthma.

CLINICAL PROCEDURE SAFETY LEVEL

Every clinician involved in the procedure is responsible for ensuring the processes for clinical procedure safety are followed. The following level applies to this procedure (click on the link for more information):
Level 1 procedure

PROCEDURE

This procedure requires mandatory compliance.

Staff Preparation

It is mandatory for staff to follow relevant: “Five moments of hand hygiene”, infection control, moving safely/safe manual handling, documentation practices and to use HAIDET for patient/carer communication: Hand hygiene Acknowledge, Introduce, Duration, Explanation, Thank you or closing comment.

Assess each patient for physical and developmental status to determine ability to perform the test and if special arrangements are required. If there is a language barrier, an interpreter may need to be used.

Ask each patient if he/she has complied with the patient preparation criteria including:

- withholding the medications that may affect the outcome of the test,
- any recent serious illnesses (e.g., myocardial infarction)

Postponement may be necessary if the patient has not met the preparation criteria.

Scientist should consult with senior scientist or ordering physician to determine if testing should proceed.

In order to properly interpret the test results, relevant clinical information (e.g., diagnosis, type of treatment) and clinical indication for ordering the test is to be provided in writing by the ordering physician.

Remove the ‘Aridol®’ components from the box and place in the container provided. This enables ease of use and continuous flow of the testing procedures.

Calibrate the pulmonary function testing system each day of use as per the laboratory manual.

Equipment Requirements

- Alcohol based hand rub
- Personal Protective Equipment
- Aridol® (Mannitol) kit (contains 1x inhalation device, capsule sachets)
- Volumatic Spacer
- Ventolin Canister (or equivalent)
- Kidney dish
- Tissues
- Digital timer

Patient Preparation
Medications

Patients should be instructed not to take any drugs that affect airway calibre and/or are considered antagonists to the challenge agent for an interval that exceeds their duration of action. These medications and the time period for withholding them prior to the test are:

Inhaled Bronchodilators:

Short acting (e.g. Salbutamol)	8 hours
Long acting (e.g. Salmeterol)	24 hours
Anticholinergic (e.g. Ipratropium bromide)	12 hours
Cromolyn Sodium (e.g. Intal)	8 hours
Nedocromil (e.g. Tilde)	8 hours
Theophylline (e.g Elixophyllin)	24 hours
Long acting Theophylline (e.g. Theo-24)	24 hours
Leukotriene modifiers (e.g. Singulair)	4 days
Antihistamines (e.g Claratyne, Telfast, Phenergan)	72 hours

Food: Ingestion of caffeine containing foods such as coffee, tea, cola and chocolate may decrease bronchial hyper responsiveness. These substances should be withheld on the day of the test.

Other factors that may confound results: Smoking and vigorous exercise should not be undertaken on the day of the test

Before the challenge, the scientist will explain and demonstrate the test requirements to the patient including inhalation of the test solutions and performance of the pulmonary function assessment required.

Pre-procedure

STOP and confirm the following before commencing the procedure:

Patient identification using three core patient identifiers (Name – family and given names, date of birth and Medical Record Number - MRN)

Procedure verification – procedure matches consent

Allergy/adverse reaction check

Anticipated critical events

Verbal consent to be obtained, written consent is not mandatory

Prerequisites
The subject must be alert and responsive to commands and must be able to sit upright in a chair.

- Bronchial provocation will be carried out only by those qualified to do so i.e. qualified scientific staff
- Prior to each days testing the spirometer will be calibrated using the 3.0 L syringe as per the appropriate section of this manual
- Each patient requires a new kit and fresh filter
- The tubing will be kept clean
- The pre-test FEV1 must be greater than 1.2 L and 55% of the predicted value
- No bronchodilators should have been used in the previous 8 hours
- No long acting bronchodilator therapy for 24 hours or antihistamines for 4 days
- A bronchodilator must be easily available

Consent form

A consent form describing the procedure should be carefully read and signed by patient or parent/legal guardian of the patient and by the scientist administering the test prior to the challenge.
A consent form should not provide information that will suggest a specific outcome.

Procedure Steps

1. Perform 5 moments of Hand Hygiene with each step as required.
2. Measure the patients' height and weight.
3. Counsel the patient as to the reasons for the test and what is expected during the test. Confirm a completed consent form is on file and check the time of the last of any bronchodilator usage.
4. Perform baseline spirometry as per laboratory manual.
5. Check FEV1 and FVC for reproducibility and minimum values as above
6. **0 mg capsule (Control)**
    a) Remove the 0mg 'Aridol' capsule from the blister, twist open the Osmohaler (as per the arrow on the device) place the capsule inside and close the device.
    b) Pierce the capsule once only by depressing the coloured buttons on either side of the inhaler.
    c) Ask the subject to put on the nose clip, and breathe through their mouth
    d) Tilt the Osmohaler at a 45o angle (mouthpiece down). Check the capsule has moved from the piercing chamber into the spinning chamber closest to the mouthpiece. You can often hear the capsule fall forward or see the capsule through the vents on each side of the device. Give the Osmohaler to the patient ensuring they keep the Osmohaler at the same angle.
    e) Ensure the patient is sitting up straight. Ask the subject to exhale (away from the Osmohaler) seal their lips around the Osmohaler mouthpiece and take a controlled rapid and deep inspiration. During successful inhalation you should hear a rattling sound as the capsule spins within the device.

f) At the end of the patients' inhalation, start a 60-second timer, and ask the subject to hold their breath for 5 seconds. When 5 seconds has passed, instruct the patient to exhale through their mouth (away from the Osmohaler) remove the nose clip and breathe normally

g) When the timer reaches 60 seconds, immediately instruct the patient to perform two acceptable FEV1 measurements. Record the highest FEV1 reading as the baseline FEV1. If the highest FEV1 is ≥10% drop from the pre-challenge FEV1 do not continue with the test.

h) Calculate the target FEV1

i) A positive 'Aridol' challenge result is achieved when the subjects FEV1 falls ≥ 15% from their baseline FEV1. To calculate the target FEV1 multiply the highest baseline (control) FEV1 obtained by 0.85. Record this value.

7. **5 mg capsule**

a) Insert 5 mg capsule into the Osmohaler and pierce as in step 6

b) Repeat steps c)-f) as above

c) Following inhalation remove the capsule from the Osmohaler and check to ensure it has been emptied completely, if not a 2nd inhalation will be required immediately

d) At 60 seconds following inhalation, immediately measure the patients FEV1 twice (acceptability criteria must be met). Use the highest of these two values to calculate the change in FEV1

e) Compare the FEV1 value at this dose to the target FEV1. If the FEV1 value is equal to or below the target value, or there has been an incremental fall of ≥ 10% from the previous dose, the challenge is positive and complete. If not, immediately proceed to the next dose step.

8. **10mg, 20mg, 40mg capsules**

Administer the 10mg, 20mg and 40mg doses following the directions given above for the 5mg dose

9. **80mg dose** (2 x 40mg capsules)

a) Insert and pierce the first of the 40mg capsules that comprise the 80mg dose.
b) The patient should inhale the dose in the same manner as previous doses, hold their breath for 5 seconds and exhale.
c) Remove the first 40mg capsule from the device and check to ensure it has been emptied completely, if not, a 2nd inhalation will be required immediately. Do this following the administration of every capsule.
d) Following inhalation, load the second 40mg capsule and offer to the subject immediately following exhalation.
e) Instruct the patient to inhale the 2nd capsule immediately to ensure that the osmotic effect of 'Aridol' is cumulative.
f) Activate timer at the end of the 2nd capsule inhalation.
g) Instruct the patient to hold their breath for 5 seconds before exhaling.
h) At 60 seconds following the inhalation of the second capsule, immediately measure the patents FEV_1 twice (acceptability criteria must be meet). Use the higher of these two values to calculate the change in FEV_1.

i) Compare the FEV_1 value at this dose to the target FEV_1. If the FEV_1 value is equal to or below the target value, or there has been an incremental fall of ≥10% from the previous dose, the challenge is positive and complete. If not, immediately proceed to the next dose step.

10. **1st x 160mg dose** (4 x 40mg capsules)
    Administer the 1st 160mg dose following the directions given above in step 8, using 4 x 40mg capsules

11. **2nd x 160mg dose** (4 x 40mg capsules)
    Administer the 2nd 160mg dose following the directions given above in step 8, using 4 x 40mg capsules

12. **3rd x 160mg dose** (4 x 40mg capsules)
    Administer the 3rd 160mg dose following the directions given above in step 8, using 4 x 40mg capsules

At the completion of this dose, 635mg has been administered. Providing a positive response has not been met, the challenge should be considered negative and complete.

13. On completion of the protocol the patient is given a 400 mcg dose of Salbutamol (via Volumatic Spacer or equivalent), administered by scientific officer.
14. Wait 10 minutes and repeat FEV1 measurement. Ensure patient has returned to within 5% of pre challenge level.
15. Record the progressive dose for a 15% decline in **FEV1** in the scientist post-test section of report

MANAGEMENT

Asthma is a condition of the airways. People with asthma have sensitive airways which react to triggers that set off their asthma. Their airways swell and get thick with mucus and the muscles around the airway squeeze tight. This makes it hard to breathe.

People with asthma can have a range of symptoms:

- Breathlessness
- Wheezing
- Tight chest
- Persistent cough – often at night, early in the morning or during/after activity

Improvement in airflow following inhalation of a bronchodilator is generally accepted as indicative of reversible airway obstruction. However, the evaluation of airway hyper-responsiveness is often indicated, especially in patients with unclear or non-specific symptoms (e.g. symptoms of asthma with normal spirometry and no bronchodilator response). Bronchial provocation (challenge) testing may be performed with a variety of agents and methods including aerosolised pharmacological agents such as Methacholine and Histamine which acts directly on airway smooth muscle, and others such as Mannitol, exercise, hypertonic saline, isocapnic hyperventilation with cold air and specific agents such as antigens, and occupational agents which acts indirectly by triggering an inflammatory response in the airway.

Paediatric Respiratory Laboratory uses the indirect method of Mannitol Challenge Test as a means to establish diagnosis in our patients.

Reasons for termination of test

- Any undue discomfort to the patient
- A fall of 15% or more in FEV_1
- Severe coughing making spirometry unreliable
- Laryngeal spasm
- Palpitations i.e. heart rate > 150bpm

SPECIAL CONSIDERATIONS

The following conditions may pose a relative danger to the patient or affect the validity of performance of challenge testing: If in doubt, check with at least one of the following: Lauren Platt (Senior Respiratory Scientist), Prof Joerg Mattes (Respiratory Physician) or contact referring doctor for clearance.

ABSOLUTE CONTRAINDICATIONS

- FEV_1 <55% predicted normal value or FEV_1<1.2L
- Recent myocardial infarction or cerebral vascular incident (within 3 months)
- Known arterial aneurysm
- Uncontrolled hypertension (systolic BP>200 or diastolic BP>100mmHg)
- Recent Pneumothorax (until fully resolved and cleared by doctor)
- An inability to understand the procedures and the implications of the challenge test.

RELATIVE CONTRAINDICATIONS (Suboptimal results likely)

- Inability to perform pulmonary function tests or poor reproducibility on PF test (e.g. FEV_1) at baseline
- Pregnancy or breast feeding
- Spirometry induced airway obstruction
- Angina, or pulmonary embolism; FVC may worsen angina and/or cause blood pressure changes
- Acute thoracic, abdominal, or cerebral aneurysm combination with severe COPD; danger of rupture due to raised intra thoracic pressure
- Recent upper respiratory tract infection (<2 weeks)
- Epilepsy requiring medication
- Exacerbation of asthma
- Recent eye surgery; raised intra ocular pressure during FVC
- Acute disorders affecting testing performance such as vomiting, diarrhoea or syncope
- Recent thoracic or abdominal surgical procedures
- Unable to sit upright for test

INFECTION CONTROL

The Osmohaler (inhaler device) is designed as SINGLE USE ONLY (one device per challenge) and should not be cleaned during the challenge. Discard the Osmohaler following each ‘Aridol’ challenge. Do not sterilise and re-use as this may compromise the integrity of subsequent test results.

Any remaining capsules should also be disposed of; these cannot be re-used for any further testing.

Dispose of filter mouthpiece and nose clip after each patient.

Alcohol wipe the containers used, and return to store cupboard to air dry.

Challenge Test Safety Precautions

- There must be a bronchodilator immediately available at all times
- All staff must be currently certified for Basic Life Support and the signs of acute asthma and how to treat it.
- An oxygen supply must be available in the laboratory area
- In the event of an acute asthma attack the test should be stopped immediately and bronchodilator administered
- Attach oximeter finger probe and monitor SpO2. Clinical review is required if SpO2 falls below 95%. If O2 rapidly falls below 90%, place patient on 5-6L oxygen
- Should the patient nor respond rapidly (< 2 mins) call for help and advice that assistance is required
- Phone #2222 and advice the operator of the problem and location.

If assistance is not called for, because the asthma attack responds to treatment, the referring doctor and respiratory physician must be notified before the patient is allowed to leave.

Test Interpretation

Bronchial Hyper responsiveness (BHR)

- Severe BHR: Positive Aridol challenge (PD_{15}) with ≤ 35mg Mannitol
- Moderate BHR: Positive Aridol challenge (PD_{15}) with >36mg and ≤155 mg Mannitol
- Mild BHR: Positive Aridol challenge (PD_{15}) with >156mg Mannitol

Post procedure

- Document procedure in patient's health care record
- Arrange post procedure tests where clinically relevant

IMPLEMENTATION, MONITORING COMPLIANCE AND AUDIT

Compliance with this document is MANDATORY

Implementation Plan – All current and future new staff will be provided with an in service as to the policies and procedures stated here. Staff will be provided formal training and will be expected to demonstrate competency in the procedure prior to the commencement of testing on patients. All staff will be provided a copy of this policy and will have access via the intranet page.

Clinical Review of this procedure will be performed annually by scientific staff performing the test for effectiveness and compliance.

CONSULTATION

Paediatric Respiratory Consultants JHCH:

- Dr Bruce Whitehead
- Prof Joerg Mattes
- Dr Jodi Hilton
- Dr Tanya Gulliver

Paediatric Respiratory Laboratory Manager – Lauren Platt

Paediatric Respiratory Laboratory Scientist – Kasey Pearce

Ambulatory Care Manager: Cathy Grahame

Paediatric Respiratory CNC JHCH: Linda Cheese, Bernadette Goddard

Pharmacists JHCH: Michelle Jenkins

APPENDICES

1. Patient Information Sheet
2. “How does Aridol® work” flowchart

BIBLIOGRAPHY

A complete reference list for this guidelines is available from the Guidelines contact person.

LINKS

www.pharmaxis.com.au
www.aridol.info

FEEDBACK

Any feedback on this document should be sent to the Contact Officer listed on the front page.

APPROVAL

CPGAG – February 2020
JHCH QUM – 12 March 2020
JHCH CQ&PCC –19 May 2020

Appendix 1: Lung Function Test Information Sheet

FACT SHEET

Approved: January 2020
Review Date January 2023

Patient/Guardian Information Sheet for Lung Function test using Mannitol

The aim of the test
To help in the review and management of your child's current condition, your doctor believes that an airway test is needed. For example, patients often go to the doctor with symptoms of shortness of breath, cough, and tightness in the chest or wheezing, that may suggest asthma. If your child's first test does not give the doctor a definite positive or negative result, you may be required to return for a more complex breathing test.

How is the test performed?
Your child will breathe in different levels of a medication called Mannitol from a device similar to an asthma puffer. Each puff will last for 1 minute. At the start of the test and after each dose, you will be asked to perform a breathing test that measures how quickly and how much you can blow out after a big breath in. The breathing test will be repeated to ensure the biggest value is recorded, before moving on to the next dose of Mannitol. If there are any large change in your child's breathing, the test will stop and your child will be offered Ventolin to reverse any symptoms that may have started. The whole process is usually finished in 45 minutes. There are no delayed or late effects.

What is Mannitol?
Mannitol is a medication used for this type of breathing test. For further information visit www.aridol.info

Are there any risks?
Testing using Mannitol is a safe and very commonly performed test in children. There have been no reported serious side effects following the use of Mannitol. Approximately 30% of patients find that the test causes mild symptoms of cough, shortness of breath, chest tightness, wheeze, headache or dizziness. These symptoms rarely cause a problem. If you do develop any such symptoms that cause discomfort or concern please immediately tell the scientist doing the test. However, if you may be pregnant, or are breast-feeding, you should inform the scientist testing you. You should also tell the scientist testing you if your child has had a recent heart attack, stroke or respiratory tract infection, are taking heart medication or has weakness in the walls of their blood vessels.

Do I have a choice?
Yes – you may refuse to do the test or stop testing at any time without affecting other testing or treatment of your child's medical condition.
If you have any problems following the test please contact your referring doctor,
the John Hunter Hospital Emergency Department (Ph: 4921 3000) or the staff at the lab (Ph: 4921 3679)

John Hunter Children's Hospital
CHILDREN, YOUNG PEOPLE AND FAMILIES

NSW GOVERNMENT Health
Hunter New England Local Health District

Appendix 2: How does Aridol work?

aridol™
MANNITOL

How does Aridol work?

Aridol™ mimics the mechanism of Exercise Induced Asthma:[1,2,3]

Respiratory Water Loss
↓
Dehydration of Airway Surface Liquid
↓
Increase in [Na^+], [Cl^-], [Ca^{++}], [K^+]
↓
Increase in Osmolarity of Airway Surface Liquid
↓
Water Moves from Cells to Restore Airway Surface Liquid
↓
Regulatory Volume Increase Follows Cell Shrinkage
↓
When Inflammation is Present Mediators are Released
↓
Prostaglandins (9α, 11β-PGF2)
Leukotrienes (LTE4)
? Histamine (N- methylhistamine)
↓
Bronchial Smooth Muscle Contraction
↓
Bronchoconstriction

ARIDOL™ WORKS HERE

DIRECT CHALLENGES (eg. methacholine/ histamine) WORK HERE

(Adapted from reference 1)

Aridol™ identifies active airway inflammation to assist in the diagnosis of asthma[3,4]