A diagnostic approach to an allergic child – role of RSV infection in asthma

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Diagnostic Approach

- Is the patient allergic?
  - Clinical – Does the history and examination fit? Does the allergy contribute to the patient’s diagnosis?
- Is there laboratory confirmation?
  - It is IgE or non-IgE mediated?
- What are the clinically relevant allergens?
  - Panel screening
  - Specific RAST
  - Patch testing
  - Provocation testing
- Monitoring of disease
Allergy or no allergy – is the question!

- History should implicate well-defined allergens.
- Symptoms & signs should fit an allergic condition.
- Repeated allergen challenge should trigger reproducible symptoms.
- Allergen withdrawal should improve these symptoms.
- Testing should confirm diagnostic hypothesis (skin, blood or challenge testing).
- Conventional allergy treatment should ameliorate symptoms.

If not - review the diagnosis!
Allergy history

- Symptoms: past and present; frequency and severity; seasonal or perennial; provoking factors
- Impact on lifestyle: absence from work or school; leisure
- Possible allergens in the home, at occupation and hobbies
- Past history of asthma, eczema, rhinitis, drug or food allergy
- Known/suspected history of previous hypersensitivities
- Previous allergy testing
- Family history of allergic disease
- Main organs: respiratory, dermatologic, ocular, nasal, GIT
- Onset and course – first onset, seasonal onset, daily onset
- Topology – symptoms worse at home, school, occupation
- Treatment: past & present; compliance; efficacy; side effects
Atopic facies

- Long pale atopic face
- Persistent facial rubbing, particularly over the submaxillary regions, by individuals with rhinitis, maxillary bone growth may be influenced.
- Rubbing commences in early childhood associated with, or result in, a high arched palate and dental malocclusion.
- Pale skin is a consequence of mild dermal oedema and abnormal capillary blood flow due to the phenomena of ‘vascular steal’.
- Skin is commonly associated with pityriasis sicca alba.
Allergic shiners and Morgan Dennie’s lines

- **Allergic shiners** – peri-orbital ecchymotic darkening beneath the eyes due to repetitive vigorous rubbing in the peri-orbital region and impaired venous return from the skin and subcutaneous tissues.

- **Morgan Dennie’s lines** – an accentuated line/secondary crease below the margin of the lower eyelid. Little is known about the aetiology, may result as a consequence of persistent peri-orbital rubbing.
Allergic mannerisms

Repetitive vertical and horizontal rubbing of the nose, also referred to as the ‘**allergic salute**’ and ‘**side swipe**’

Repetitive sneezing, and continual facial distortion

Pale, clear crease at the junction of nasal cartilage and bone is called the **nasal crease**, due to upward ‘folding’ with each allergic salute.

Postnasal drip leads to ‘**throat clearing**’ noises and a ‘**brassy**’ sounding cough.

Continuous mouth breathing leading to the ‘**allergic gape**’
Intranasal examination

- otoscope, or ideally, a flexible nasal endoscope.
- normal anatomical structures and mucosa
- In allergic rhinitis the nasal turbinates are classically enlarged and ‘boggy’ and may appear pale or bluish-grey in colour, Thin watery nasal secretions
- mucosal erythema non-specific
- Hansel’s stain for eosinophils
Further examination

- Skin – urticaria, angioedema, dermatitis, lichenification
- Eyes – conjunctival hyperaema, chemosis, giant papillae, vernal keratoconjunctivitis
- Detailed ear, nose and throat examination
- Chest evaluation
Diagnosing Allergy

**ATOPIK SYNDROMES**
- Allergic Asthma
- Allergic Rhinitis
- Atopic Eczema
- Allergic conjunctivitis
- Urticaria / Angioedema
- Anaphylaxis

**SPECIFIC ALLERGY**
- Food Allergy
- Insect Allergy
- Latex Allergy
- Drug Allergy
‘Testers’ vs ‘Treaters’ : The need to ‘test’

- Testers - treatment can be more focused, include specific allergen vs. Treaters – guess the likely allergen on epidemiology

Which test?

- Total IgE & Total Eosinophil count vs. CAST
- IgE panels (Phadiatop, FX5) vs. Skin prick testing (in vivo)
- Specific IgE (RAST) (in vitro)
- Provocation / Challenge Testing
- Patch testing
Is this possibly allergy? Total IgE

- **Screening test** but its use may be limited because:
  - reference values are not available for all populations & overlap between normal /abnormal
  - it has poor sensitivity 50-60% and specificity
  - non-allergic conditions can produce elevations e.g. helminthic and parasitic disease, hyperIgE syndrome, HIV, ABPA
  - may be normal in severe allergy in a small organ e.g. the nose

- Total IgE > mean + 1 standard deviation for age MAY indicate allergy
  - In small children under 3 years
  - When parasite infestation is not common
  - Diagnosis and follow up of ABPA
  - In patients who appear Allergic in spite of a negative specific IgE
Eosinophil count

- Can be normal or slightly elevated in atopic individuals (normal < 400 cell/mm³)
- Marked eosinophilia (>1500) more likely to be due to parasitic disease
- More useful if eosinophils present in specific site e.g. nasal fluid in Allergic Rhinitis (Hansel’s stain)
CAP RAST (CAST)

- Sensitivity to many environmental agents can only be confirmed by challenge tests, which are usually tedious and in some instances could be dangerous.

- **Majority of Non-IgE mediated** adverse reactions to foods and drugs in clinical practice. The **cellular antigen stimulation test** (CAST) is useful for detecting these non-IgE-mediated sensitivities.

- The **CAST** depends on the exposure of interleukin 3 (IL-3) primed fresh basophils to different concentrations of an allergen, drug or chemical. Basophils which are sensitive to such exposure release sulphido leukotrienes into the media which are measured by an ELISA test.

- The CAST thus measures both IgE- and non-IgE-mediated leukotriene release in the ELISA.
Which allergen to test for?

- First onset
  - < 3yrs + excema/urticaria – ingested + contact allergens or > 3yrs – inhalants

- Seasonality
  - late spring/summer – grass/tree or late summer/autumn – pollen, mould

- Daily onset
  - night time symptoms – House dust mite or day time symptoms – pollens

- Coastal-High humidity: Durban/Cape town-HDM, cockroach, mould

- Inland or Highveld – grasses

- Symptoms worse indoors or during wet months – mould allergy, cat or dog allergy, HDM, Pillows and bedcovers – feathers

- Perennial – test for house dust mite, animal protein

- Seasonal - Pollen calendar for South Africa
  - August: grasses, pollen and tree
  - September to February: Grasses (rye, Bermuda and Eragrostis)
  - March to May: Weed pollens (plantain and cosmos), mould spores
Technique & Interpretation of SPT

- Universally standardised lancets and purified allergen extracts
- Usual site for testing is the inner (volar) aspect of the forearm
- Inhalant allergen testing include house-dust mite, cat dander, dog dander, tree pollens, grass pollens and mould spores.
- Food allergens include cow’s milk, hen’s egg, wheat flour, soy, codfish and peanut.
- Positive and negative control test to assess normal skin reactivity
- A positive result to a specific allergen or mix is indicated by a mean wheal diameter measuring \(3 \text{ mm or } >\) negative control
- Associated flare or erythema is not used to gauge sensitisation.
- The severity of an allergic reaction cannot be accurately predicted by the size of the wheal alone.
Skin Prick Testing

ADVANTAGES

- Relatively safe and quick
- Immediate results (15-20min)
- Patient involvement
- Relatively inexpensive
- Can be used as young as 4 months if patient tolerant

DISADVANTAGES

- Risk of systemic reaction
- Cannot be used if previous anaphylaxis or severe reaction
- Needs ‘normal’ skin
- Antihistamines, TCA, steroids withdrawn within 72hrs
- False positives - dermatographism
**Likelihood ratios - SPT**

*Skin prick testing: 100% positive predictive value (PPV) for food allergy*

<table>
<thead>
<tr>
<th>Food allergen</th>
<th>100% PPV &lt; 2 yrs (Wheal diameter)</th>
<th>100% PPV &gt; 2 yrs (Wheal diameter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cow’s milk</td>
<td>6 mm</td>
<td>&gt;8 mm</td>
</tr>
<tr>
<td>Hen’s egg</td>
<td>5 mm</td>
<td>&gt;7 mm</td>
</tr>
<tr>
<td>Peanut</td>
<td>4 mm</td>
<td>&gt;8 mm</td>
</tr>
</tbody>
</table>

Source: Sporik *et al*.15
Phadiatop & Food Panels

- Important when no specific allergen implicated & cost effective

- **Phadiotop**
  - for common inhalant allergens with sensitivity of 100% and specificity of 90% in SA children. Does not detect and is not influenced by parasitic IgE.

- **Perennial allergy**
  - House-dust mite, Cat, Dog, Mould mix, Cockroach (Durban), F x 5 (young children)

- **Seasonal allergy**
  - G x 2 mix (including Bermuda), Tree mix, Acacia (savannah regions), Weeds (English plantain), Western blotting for individual indigenous grass sensitivities

- Optigen Inhalant 20 allergens

- **FX food panels**
  - Cross-reactivity between epitopes – test group e.g. **fx1** nut allergen panel (peanut, brazil nut, almond, hazelnut, coconut), **fx2** seafood panel (cod, tuna, shrimp, blue mussel, salmon) and **fx3** cereal panel (wheat, oat, maize, sesame, buckwheat). **fx5** common e.g. Cow’s milk, egg, wheat, soy, codfish, peanut
  - **fx5** is highly efficient (about 90%) as an indicator of atopy at 3 years age, the sensitivity drops as the antibodies to egg and/or milk decrease or disappear

- **Universal Panel 20** – 12 inhalants and 8 food allergens

- **Disadvantages** no identification of the specific aero-or food allergens and cost.
Specific IgE testing

- Over 550 different allergens are available for allergy testing
- Useful if few implicated allergens on history
- More expensive
- Safe
- No need to withdraw medication
- Not influenced by skin disease (e.g. eczema)
- Larger range of allergens
- Result delayed
- Lends itself to over testing (knee-jerk ticking of request form)
### Interpreting specific IgE

<table>
<thead>
<tr>
<th>IgE level (kU/l)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.1</td>
<td>Below detectable levels</td>
</tr>
<tr>
<td>0.35 – 0.69</td>
<td>Low</td>
</tr>
<tr>
<td>0.70 – 3.49</td>
<td>Moderate</td>
</tr>
<tr>
<td>3.50 – 17.49</td>
<td>High</td>
</tr>
<tr>
<td>17.50 – 49.99</td>
<td>Very high</td>
</tr>
<tr>
<td>50 - 100</td>
<td>Very high</td>
</tr>
<tr>
<td>&gt;100</td>
<td>Extremely high</td>
</tr>
</tbody>
</table>

#### History

*History* plays an important role in allergy diagnosis, and tests **must** be interpreted within the context of patients’ symptoms. Patients may have positive tests **without clinically expressing** their allergy. A highly positive test will not **necessarily predict the severity** of a reaction.

In the same way, a **low specific IgE level** does not necessarily mean that a patient’s symptoms will be mild.
### Clinical decision end points

**Food-specific IgE concentration (kU/I) clinical decision points**

<table>
<thead>
<tr>
<th></th>
<th>Egg</th>
<th>Milk</th>
<th>Peanut</th>
<th>Fish</th>
<th>Soy</th>
<th>Wheat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactive if ≥</td>
<td>7</td>
<td>15</td>
<td>14</td>
<td>20</td>
<td>65</td>
<td>80</td>
</tr>
<tr>
<td>(no challenge needed)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Possibly reactive</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>(physician challenge)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unlikely reactive if &lt;</td>
<td>0.35</td>
<td>0.35</td>
<td>0.35</td>
<td>0.35</td>
<td>0.35</td>
<td>0.35</td>
</tr>
<tr>
<td>(home challenged)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sampson et al. Food allergy. JACI 2003; 111(2): 5540-5547
Atopy Patch Testing

- diagnosis of aero-allergen- and contact allergen-induced allergic reactions.
- diagnosis of immediate and/or delayed-onset food induced allergic reactions.
- technically demanding and time-consuming for staff and patient alike with patients needing to return some 72 hours post APT
- Useful for non-IgE mediated allergy
Challenge tests

- Food challenges – double blind placebo controlled challenge
gold standard for food allergy

- Histamine / Methacholine challenge test – spasmogens may be
used for difficult to diagnose asthma - > 20% drop in FEV1
post exposure

- Exercise challenge Test – exercise for 6 minutes, fall in post-
exercise FEV1 / PEFR > 15% diagnostic of EIA
Monitoring Allergic inflammation

- Eosinophil Cationic Protein
- Mast cell tryptase
- Histamine assays
- Allergy cytokine assays
- Antibodies to IgE receptors
The initial consideration before investigating

**HISTORY AND EXAMINATION**

**INHALANT**
- Total IgE – exit test
- **Skin Prick test**
- RAST - multi-allergen
  - Phadiatop
- Blood – individual allergen **specific IgE**
- Provocation/Challenge

**INGESTANT**
- **Total IgE**
  - < 2yrs – RAST
  - Paediatric food mix
  - > 2yrs – individual allergens
    - multiallergen

- **Provocation / Challenge tests**
  - Foods / preservatives / drugs **CAST assay**

**INNOCULANT**
- individual allergen – **history** important
  - Most common **CAP RAST** to bee venom and penicillin.
  - Alternative **skin testing**

**CONTACT**
- 95 % not IgE mediated
- Chemical hypersensitivity
- **Patch Testing** for suspected offending agent by dermatologist
Asthma incidence post early Bronchiolitis

- Long-term outcome for bronchial asthma was determined up to 8 to 10 years in children after early bronchiolitis
- 62 children hospitalized with early-childhood bronchiolitis, 29 children hospitalized with early-childhood pneumonia, and 52 control children
- Compared to controls, occurrence of bronchial asthma was increased (P<0.001) in early-childhood bronchiolitis

RSV-Induced Bronchiolitis is Associated With the Development of Asthma

In a study of 140 children, the incidence of asthma at age 7.5 years was higher in children who had been infected with RSV in infancy compared with matched controls.

Children with asthma at age 7.5 years (%)

- RSV (n=47): 30%
- Control (n=93): 3%

207 children with mild RSV LRI vs. Controls had no LRI in the first 3 years of life.

Risk for frequent wheeze was still significantly increased at 11 years ($p \leq 0.01$) in RSV LRI group.

Role of Palivizumab: Mechanism of Action

- Palivizumab is a humanized monoclonal antibody that binds the F protein of RSV
- Palivizumab blocks the fusion of infected cells
- Reduces viral activity and cell-to-cell transmission of the virus, thereby reducing the incidence of lower respiratory tract infection

Pivotal Efficacy trial

Palivizumab Prophylaxis Decreases RSV Hospitalizations in Prems

RSV hospitalization rates by subgroup

<table>
<thead>
<tr>
<th>Category</th>
<th>Group</th>
<th>Hospitalization Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>Placebo: 1996-1997 IMpact-RSV trial (n=500)</td>
<td>10.6%</td>
</tr>
<tr>
<td></td>
<td>Synagis®: 1996-1997 IMpact-RSV trial (n=1002)</td>
<td>4.8%</td>
</tr>
<tr>
<td>All &lt;32 weeks GA</td>
<td>Placebo: 1996-1997 IMpact-RSV trial (n=500)</td>
<td>11.0%</td>
</tr>
<tr>
<td></td>
<td>Synagis®: 1996-1997 IMpact-RSV trial (n=1002)</td>
<td>5.8%</td>
</tr>
<tr>
<td>All 32-36 weeks GA</td>
<td>Placebo: 1996-1997 IMpact-RSV trial (n=500)</td>
<td>9.8%</td>
</tr>
<tr>
<td></td>
<td>Synagis®: 1996-1997 IMpact-RSV trial (n=1002)</td>
<td>2.0%</td>
</tr>
</tbody>
</table>

% REDUCTION

- All patients: 55%
- All <32 weeks GA: 47%
- All 32-36 weeks GA: 80%
## ADVERSE REACTIONS

<table>
<thead>
<tr>
<th>FEATURES</th>
<th>SYNAGIS</th>
<th>PLACEBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOCAL REACTIONS</td>
<td>11%</td>
<td>10%</td>
</tr>
<tr>
<td>FEVER</td>
<td>2.7%</td>
<td>1.8%</td>
</tr>
<tr>
<td>RASH</td>
<td>3.0%</td>
<td>2.8%</td>
</tr>
<tr>
<td>DEATHS</td>
<td>4%*</td>
<td>5%</td>
</tr>
</tbody>
</table>

* Not related to synagis
CONCLUSIONS FROM IMPACT STUDY

In a randomised, double-blind study involving 1,502 infants aged <2 years with chronic lung disease, administration of palivizumab:

- **EFFICACY**
  - 55% ↓ hospitalization <35/52 - 39% in BPD
  - 78% non BPD
  - 57% ↓ admission to ICU
  - 2 x ↓ days in hospital

- **SUBANALYSIS** - all countries efficacy confirmed

- **SAFETY** - CONFIRMED in high risk cases

Cost-benefit analysis did not demonstrate an overall saving in hospitalisation considering the costs of therapy for all at-risk children

The Current SA Guidelines

Table V. Indications for palivizumab

1. Premature infants of gestational age <32 weeks at birth. Prophylaxis should be continued until the earlier of:
   • 6 months of chronological age, or
   • the end of the RSV season (last dose in July)

2. Premature infants of gestational age 32 - 36 weeks at birth. Prophylaxis should be continued until the earlier of:
   • 3 months of chronological age, or
   • the end of the RSV season (last dose in July)

3. Children of any gestation who are <24 months of age at the start of the RSV season with any of the following: chronic lung disease of prematurity, chronic lung disease, primary immunodeficiency, cyanotic congenital heart disease. Prophylaxis should be used for 5 months beginning in February in most areas of South Africa except for KwaZulu-Natal, where it should be started in December

4. High-risk premature infants should commence their prophylaxis while still in hospital
Guideline based on risks

- Effectiveness only when high chance of acquiring RSV and host impairments resulting in serious illness
- Gestational age <32 weeks vs 32-36 weeks
- Chronological age <3 mths, <6 mths, <24 months
- Seasonality- Durban vs. CT vs. Johannesburg
- Risk factors: Chronic lung disease, chronic heart disease, asthma, post ICU
- Costs- expensive – if cheap will be given to all as RSV is a common disease but low MR/MB in low risk
RSV HOSPITALIZATION - BY SUBGROUP (I) IMPACT RSV trial

8.1% 1.8%
9.8% 2.0%
10.0% 1.8%

All Preterm No BPD
All Preterm 32-35 Weeks
Preterm 32-35 Weeks No BPD

78% 80% 82%

Placebo Synagis

IMPACT, Pediatrics 2000
Seasonality of RSV outbreaks varies
1. In Cape Town, a biennial peak is seen.
2. In Gauteng, the epidemic begins in late February and ends in August.
3. In Durban, a peak between February and March, during the rainy season.
RSV may be identified throughout the year in HIV infected children because of prolonged shedding of the virus up to 100 days post-infection, compared to shedding of 5-7 days in HIV uninfected children.
## PALIVIZUMAB PROPHYLAXIS IN CHILDREN WITH CONGENITAL HEART

<table>
<thead>
<tr>
<th></th>
<th>Synagis N=639</th>
<th>Placebo N=648</th>
<th>Reduction (95% C.I.)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSV hospitalization</td>
<td>34 (5%)</td>
<td>63 (10%)</td>
<td>45 (23.67)</td>
<td>0.003</td>
</tr>
<tr>
<td>Days RSV hospitalization/100*</td>
<td>57</td>
<td>129</td>
<td>56</td>
<td>0.003</td>
</tr>
<tr>
<td>RSV days-supp. Oxygen/100*</td>
<td>28</td>
<td>102</td>
<td>73</td>
<td>0.014</td>
</tr>
<tr>
<td>ICU admission</td>
<td>13 (2%)</td>
<td>24 (4%)</td>
<td>46</td>
<td>0.094</td>
</tr>
<tr>
<td>Days ICU stay/100*</td>
<td>15.9</td>
<td>71.2</td>
<td>78</td>
<td>0.080</td>
</tr>
<tr>
<td>Days IPPV/100</td>
<td>6.5</td>
<td>54.7</td>
<td>88</td>
<td>0.224</td>
</tr>
</tbody>
</table>

*per 100 children

Feltes TF J Pediatr 2003
Synagis Prophylaxis Decreases RSV Hospitalization in Infants With Haemo-dynamically Significant CHD

45% relative reduction ($P=0.003$)

- Placebo (n=648): 9.7% (63/648)
- Synagis® (palivizumab) (n=639): 5.3% (34/639)

CHD and RSV Severity

- Increased risk for ICU and mechanical ventilation

- In one prospective study of RSV infection in CHD vs. healthy patients
  - ICU (63% vs. 14%, p<0.001)
  - Mechanical ventilation (22% vs. 5%, p<0.01)

- Canadian epidemiological study of CHD
  - 33% ICU admission
  - 19% mechanical ventilation

MacDonald, NEJM, 1982, Navas, J of Pediatrics, 1992
Synagis Reduces Recurrent Wheeze by 50%

Observations:
- Caretaker-reported recurrent wheeze:
  - SYNAGi5® (n=191): 13%*
  - Control (n=230): 26%
- Physician-diagnosed recurrent wheeze:
  - SYNAGi5® (n=191): 8%
  - Control (n=230): 16%

*P-value 0.001 between SYNAGi5® and control
†P-value 0.001 between SYNAGi5® and control

Prospective cohort study of the incidence of caretaker-reported and physician-diagnosed wheezing among 191 premature infants who received palivizumab (SYNAGi5® prophylaxis) and 230 age/gestation age-matched controls who did not receive SYNAGi5® prophylaxis.
Systematic review and health modelling of use of Palivizumab UK experience

- Palivizumab does not meet conventional UK standards of cost effectiveness at 30000 pounds/ QALY in the UK
- Studied in different high risk subgroups –prems, CLD, CHD
- Compared palivizumab vs. no prophylaxis in children without CLD/CHD, with CLD, with acyanotic and cyanotic CHD
- N = 13 studies and 16128 subjects
- 24w GA + <6 Weeks CA @ start of RSV season + 2 risk factors yes
- <32w GA+ >9m CA @ start of season with no risk factors- no
- CLD <28w GA+ <6 M CA @ start but not > 21 m- yes
- ACHD <24 w GA + <21 m CA @ start of season – yes
- CCHD<24 w GA +<12 m CA at start of the season- yes

Unselected use is not cost effective but cost effective subgroup - No CLD/ CHD + 2 OTHER risk factors besides GA & CA
CLD or CHD don’t need other risk factors - Wang D et al Health tech assess 2011
Take home message

- RSV infection is a common problem with significant mortality in high risk groups
- Seasonality is variable across different regions
- Short-term consequences include increased ICU & hospitalization admission, need for oxygen in high risk
- Current therapeutic options are ineffective
- PALIVIZUMAB is
  - effective for prems, CLD or CHD
  - cost effective for patients with CHD or CLD
  - cost effective in premature infants with least 2 other risk factors

ICU = intensive care unit.