Immunodeficiency and RARS: When to Suspect and What (Not) To Do

The NOSE symposium

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Disclosures

• Serve on clinical events adjudication committee for Pharmacosmos
Learning Objectives

• Known when you should suspect primary immunodeficiency (PID) in your RARS patients

• Know the initial workup for PID in RARS patients

• Distinguish humoral immune deficiencies relevant to patients with RARS, including CVID, IgA deficiency, and secondary hypogammaglobulinemia
Prevalence of antibody deficiency

31.6% of CRS patients w/PID

35% of CRS patients w/PID
Guidelines-based medicine

Clinical Practice Guideline (Update): Adult Sinusitis

Richard M. Rosenfeld, MD, MPH, Jay F. Piccirillo, MD, Sujana S. Chandrasekhar, MD, Itzhak Brook, MD, MSc, Kaparaboyina Ashok Kumar, MD, FRCS, Maggie Kramper, RN, FNP, Richard R. Orlandi, MD, James N. Palmer, MD, Zara M. Patel, MD, Anju Peters, MD, Sandra A. Walsh, and Maureen D. Corrigan

Testing for Immune Function

Immunodeficiency should be considered in patients with CRS or recurrent ARS when aggressive management has failed or when sinusitis is associated with otitis media, bronchiectasis, or pneumonia.203,205

9. Patients with RARS should have objective evidence of disease by anterior nasal examination, nasal endoscopy, or sinus CT scan. They should be evaluated for underlying inflammation, allergy, immunodeficiency, and anatomic abnormalities. Culture of the drainage is appropriate.
When to Suspect PID
Red Flags for PID

<table>
<thead>
<tr>
<th>Red Flags for PID</th>
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<tbody>
<tr>
<td>2 Two or more new sinus infections within 1 year, in the absence of allergy.</td>
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</table>
Red Flags for PID

10 Warning Signs of Primary Immunodeficiency Disorder

If you or someone you know is affected by two or more of the following warning signs, speak to a physician about the possible presence of an underlying Primary Immunodeficiency.

1. Four or more new ear infections within 1 year.
2. Two or more serious sinus infections within 1 year.
3. Two or more months on antibiotics with little affect.
4. Two or more pneumonias within 1 year.
5. Failure of an infant to gain weight or grow normally.
6. Recurrent, deep skin or organ abscesses.
7. Persistent throat in mouth or fungal infection on skin.
8. Need for intravenous antibiotics to clear infections.
9. Two or more deep-seated infections including sepsisemia.
10. A family history of PID.

Primary Immunodeficiencies (PIDs) are more common than you think. Often, they come in the disguise of other common illnesses, from minor infections to serious cases of pneumonia. For this reason, the PID Community recommends that all patients affected by two or more of the 10 Warning Signs should be tested for an underlying PID.
It’s probably not PID if ...

• **RARS in isolation** is likely due to:
  – Allergic rhinitis
  – Inadequately treated ABRS
  – CRS
  – Local anatomic defect
  – Another diagnosis (e.g. migraine HA, VRS)

• And is NOT likely to reflect:
  – Primary Immunodeficiency
When to suspect PID

• After you have CONFIRMED the diagnosis of recurrent ABRS

• In patients with infections in more than one organ system (i.e. not just RARS/CRS, but ALSO otitis, skin infections, GI infections, pneumonia, etc)

• Medically atypical or refractory disease (out of the norm for your practice)
Initial Work-Up for PID
**Initial Work-Up for PID**

### Labs to order
- CBC/diff
- HIV Ab
- IgG, IgA, IgM, IgE
- Tetanus IgG
- S. typhi IgG pre/post vaccine titers*

### Labs NOT to order
- S. pneumo IgG titers**
- Diphtheria IgG
- H. influenzae IgG
- IgG subclasses
- CH50/AH50 in adult-onset disease

* If you have the vaccine in stock and ability to send labs to Medical College of Wisconsin

** Unless you are 100% confident in your ability to interpret them!***

*** Nobody is 100% confident in how to interpret them
IgG, IgA, IgM

- By definition, 2.5% of the healthy population is above and 2.5% is below the “normal” range
  - An IgG that is 1 mg/dl below “normal” is not significant
IgG, IgA, IgM

- Normal ranges vary widely between labs!

<table>
<thead>
<tr>
<th></th>
<th>IgG (mg/dl)</th>
<th>IgA (mg/dl)</th>
<th>IgM (mg/dl)</th>
<th>IgE (IU/ml)</th>
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<tbody>
<tr>
<td><strong>ARUP Laboratories</strong></td>
<td>768-1632</td>
<td>68-408</td>
<td>35-263</td>
<td>0-214</td>
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<td><strong>LabCorp</strong></td>
<td>700-1600</td>
<td>91-414</td>
<td>40-230</td>
<td>0-100</td>
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<td><strong>Mayo Medical</strong></td>
<td>767-1590</td>
<td>61-356</td>
<td>37-286</td>
<td>13.2-127.0</td>
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<td><strong>Laboratories</strong></td>
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<td><strong>Quest Diagnostics</strong></td>
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<td>81-463</td>
<td>48-271</td>
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<td><strong>University of</strong></td>
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<td><strong>Virginia Health</strong></td>
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<td><strong>Systems (old)</strong></td>
<td></td>
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<tr>
<td><strong>UVA (new)</strong></td>
<td>552-1631</td>
<td>69-517</td>
<td>33-293</td>
<td>10-180</td>
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<tr>
<td><strong>Viracor Eurofins</strong></td>
<td>625-1319</td>
<td>72-391</td>
<td>44-247</td>
<td>3-96</td>
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<tr>
<td><strong>Clinical Diagnostics</strong></td>
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IgG subclasses

• Significant decrease in one or more IgG subclasses with a NORMAL total IgG

• Controversial if this is a “true” PID
  – Up to 20% of the population have “low” levels of one or more subclasses
  – Most people with subclass deficiency do not have increased infection

IgG subclasses should not be checked routinely in immunodeficiency evaluation as the connection of IgG subclass deficiency to recurrent or CRS is controversial, and the clinical significance of abnormal IgG subclasses in patients with recurrent infections is unclear.
Further Work-Up

Now what?
Assessing response to vaccines

- Pneumococcal conjugate
- *Haemophilus influenzae* B
- Diphtheria and tetanus
- Meningococcal, hepatitis A, hepatitis B, rabies, varicella, measles/mumps/rubella

- Pneumococcal polysaccharide
- *S. typhi* polysaccharide

Figure adapted from Janeway’s Immunobiology: The Immune System in Health and Disease
Response to protein/conjugated vaccines

- Impaired typically only in more severe forms of immunodeficiency
- An absent response to tetanus (assuming vaccination within 10 years) is always abnormal
- Poor antibody response does not necessarily represent immunodeficiency
  - Varicella
  - Diphtheria
  - Haemophilus influenzae B
  - Hepatitis B
  - PCV-13 (especially serotypes 6B, 9V, 23F)
Response to polysaccharide vaccines
Pneumococcal polysaccharide vaccine (PPSV-23)

• Current recommendations for PPSV-23
  – Intermediate risk adults 19-64 years
  – All adults 65 years and up

• Current recommendations for PCV-13
  – All children at 2, 4, 6, and 12-15 months
    • From 2000-2010, was PCV-7
    • Prior to 2000, no routine vaccination
  – High risk adults 19-64 years
  – All adults 65 years and up
Pneumococcal vaccines

• Almost everyone has gotten some combination of PCV-7, PCV-13 or PPSV23

• Need to know exactly **when** they got the vaccine and **which** vaccine they got

• The definition of a “normal” response is controversial

• Lots of healthy people have “abnormal” responses anyway
We are all immune deficient!

- Study of 98 healthy adults (ages 18-92 years) without history of recurrent infections
  - 20.4% had abnormal response to the PPSV-23 (45% mild, 40% moderate, 15% severe phenotype)
Other options
S. Typhi IgG

• Newer studies support specificity of assessing immunization response with *Salmonella typhi* PS vaccine to assess antibody response

• Advantages:
  – inexpensive
  – neoantigen for most of USA
  – unlikely to be present in Ig replacement in USA

• IgG can be readily assessed by EIA sent to Wisconsin lab
  – ratio post-/pre- IgG ≥2 compellingly demonstrates normal response
S. Typhi IgG

Specific Ab to Typhi Vaccine Abnormal in PIDs

<table>
<thead>
<tr>
<th>Group</th>
<th>Control (n=22)</th>
<th>Known PID (n=30)</th>
<th>Possible ID (n=29)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Showing Normal Response</td>
<td>100% (n=22)</td>
<td>0% (n=0)</td>
<td>72.4% (n=21)</td>
<td>&lt;0.0001</td>
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PPV – 87.5%
NPV – 100%
Diseases to consider

Possibilities
Spectrum of disease

- IgG subclass deficiency
- IgA deficiency
- Specific antibody deficiency
- CVID
- XLA
- Combined immunodeficiency
IgA deficiency

- Low/undetectable IgA with normal IgG, IgM
- Most common antibody deficiency (1:400 live births)
- **Most subjects are normal** (no phenotype) and often only incidentally diagnosed
- Some subjects with increased sinopulmonary infections or increased GI infections
- Can present with increased incidence of allergic and autoimmune disease
Specific antibody deficiency

- Normal Ig levels

- Abnormal antibody response to natural infection or immunization, esp. with polysaccharide antigens
Specific Antibody Deficiency in CRS

CRS evaluated for SAD N=239

- SAD N=56 (23%)
  - Asthma N=40 (71%)
  - AR N=38 (68%)
  - Ig Therapy N=10 (18%)

- NB and Responders N=183 (77%)
  - Asthma N=116 (63%)
  - AR N=135 (74%)
  - Ig Therapy N=0

- CRS
  - CRSwNP N=12 (21%)
  - CRSsNP N=44 (79%)

- CRSwNP N=50 (27%)

- CRSsNP N=133 (73%)

FIGURE 2. Numbers of protective pre- and postpolysaccharide vaccine immunization titers were lower in subjects with SAD compared with responders and subjects with normal baseline.
Common Variable Immunodeficiency (CVID)

• Recurrent infections – AND –
• Low IgG + low IgA and/or IgM
  – And in our opinion, low IgE
• Age >4 years
• No other explanation for low antibody levels
• Impaired antibody response
Treatment options
Non-Surgical Management

- Control of allergic disease
- Minimizing smoke exposure
- Aggressive hygiene measures (saline irrigation)
- Age appropriate vaccination
- Early institution of culture-directed antibiotics
- Rotating prophylactic antibiotics
• Adults
  – Amoxicillin 500 mg daily
  – Bactrim DS daily
  – Azithromycin 250 mg M/W/F
  – Clarithromycin 500 mg daily
  – Doxycyline 100 mg daily

• Children
  – Amoxicillin 20 mg/kg daily
  – Bactrim 5 mg/kg daily
  – Azithromycin 5 mg/kg M/W/F
  – Clarithromycin 7.5 mg/kg daily
  – Doxycycline (8 years and up) 25-50 mg daily

• Rotate monthly
  – But no proof this is needed

• Consider only Sept-Feb dosing

• Probiotics while on antibiotics
• **IVIG**
  – Dose of 0.4-0.6 g/kg IV q28days
  – Can be given at free-standing infusion centers, clinics, hospital based infusion centers
  – More side effects than SCIG
  – Need for reliable IV access (*but NO PORTS*)

• **SCIG**
  – Dose divided into daily, 3x/weekly, weekly, biweekly or monthly infusions depending on product and patient preferences
  – Well tolerated
  – Less peaks/troughs means less “wear-off” effect
Judicious use of IgRT

- **Blood product** pooled from >10,000 donors
- Limited resource – recent shortages
- Very costly to the healthcare system as a whole ($50-70,000 a year)
- Side effects are not inconsequential
Primary Immunodeficiency Clinic

- Weekly adult and pediatric outpatient clinics at UVA
- Adult clinic in conjunction with Dr. Larry Borish
- For appointments
  - 434-924-5321 kids
  - 434-924-2227 adults