PIDs and Susceptibility to Mycobacterial Diseases

...IL-12/IL-23/IFNγ pathway and beyond

CIS Summer School 2015, Miami, October 2015
The immunodeficiency disorders are a diverse group of illnesses that, as a result of one or more abnormalities of the immune system, increase susceptibility to infection. The primary immunodeficiencies are...genetic disorders with characteristic inheritance patterns.”
PIDs and Susceptibility to Mycobacterial Diseases
The genus *mycobacteria* has followed the development of the world since thousands of years ago…

The first registry of a mammal infected with *mycobacteria* comes from 17,000 years ago: Osteomyelitic lesions were detected and MTB-complex DNA was isolated from a metacarpal bone of an American Pleistocene bison (*CID 2001, 33:305-11*)
Among humans, MTB-complex DNA was isolated from 5,000 year-old Egyptian mummies, as well as from 3,500 year-old Peruvian mummies (*Lancet* 1997, 350:1404; *PNAS* 1994, 91:2091-11)
PIDs and Susceptibility to Mycobacterial Diseases

Relative Virulence

- M. tuberculosis
- M. bovis
- M. kansasii
- M. leprae
- Bacille Calmette-Guerin
- M. avium complex
- M. abscessus
- M. fortuitum
- M. smegmatis
- M. gordonae
# PIDS and Susceptibility to Mycobacterial Diseases

<table>
<thead>
<tr>
<th></th>
<th>Bacterial</th>
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<th>Fungal</th>
<th>Micobact.</th>
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**PIDs and Susceptibility to Mycobacterial Diseases**

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</tbody>
</table>
PID and Susceptibility to Mycobacterial Diseases

- **SCID**
  
  *(Severe Combined Immunodeficiency)*

  - B(-)
  
  - NK(-)
  
  - NK(+) - RAG1/RAG2 (rr)
  
  - Artemis, Ligase IV, Cernunnos (rs), PKs
  
  - γC (XL)
  
  - Jak3 (AR)
  
  - CD45 (AR)
  
  - IL-7Rα
  
  - CD3δ
  
  - CD3ζ

- Incidence: ~1/50,000 newborns (based on NBS screening data)
PIDs and Susceptibility to Mycobacterial Diseases

- CGD
  *(Chronic Granulomatous Disease)*

- Incidence: ~1/200,000 newborns (5 genetic forms altogether)
PIDs and Susceptibility to Mycobacterial Diseases

- MSMD
  (Mendelian Susceptibility to Mycobacterial Diseases)

- IFNGR1
- IFNGR2
- IL12B
- IL12RB1
- STAT1
- NEMO
- TYK2
- ISG15
- IRF8
- RORGC
- IKBA

...and soon to come: IL12RB2, NRAMP, SPPL2A,...

- Incidence: ~1/100,000 newborns (all genetic forms together)
PIDs and Susceptibility to Mycobacterial Diseases

**IL-12/IL-23/IFNγ pathway**
PID\textsubscript{S} and Susceptibility to Mycobacterial Diseases
Bacillus Calmette-Guérin (BCG)

- 1908-1921: after 13 years and 231, 3-week-subcultures in a medium with potato slices + glycerol + beef bile, the attenuated M. bovis-BCG vaccine strain was generated
- 1948, massive vaccinations; >4 billion vaccines applied since 1960
- Originally designed to protect against TB, BCG vaccine does not prevent primary TB infection or TB reactivation of latent pulmonary infection, the principal source of bacillary spread in the community
- BCG immunization coverage worldwide: ~88%
- World Population: ~7 billion inhabitants
- World BCG coverage: ~88% (~6.3 billion, mostly NB)
- World birth rate: ~134 million births/year

SCID: ~2600 NB/y; ~2,300 BCG vaccinated
CGD: ~650 NB/y; ~600 BCG vaccinated
MSMD: ~1,300 NB/y; ~1,100 BCG vaccinated

Date of slide: 23 August 2006
BCG in Primary Immunodeficiencies

• Clinical presentation
  - Localized regional
  - Localized extra regional
  - Disseminated

• Family history/Inheritance patterns
  - AR: IFNGR1, IFNGR2, STAT1, IL12B, IL12RB1, TYK2, AR SCID, AR CGD, IRF8, ISG15, SCID
  - AD: IFNGR1, STAT1, IFNGR2, IRF8
  - XR: CGD, SCID
  - XD: NEMO
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  XR: CGD, SCID
  XD: *NEMO*
PIDs and Susceptibility to Mycobacterial Diseases

Evaluation of PID with increased susceptibility to BCG infections

• HIV infection
  Serology, maternal serology, antigenemia, PCR

• Predominantly T cell deficiencies
  SCID; CBC+diff, Ly subpopulations and Ly proliferation tests

• Predominantly Phagocytic cell deficiencies
  CGD; respiratory burst evaluation, DHR test, NBT test
PIIDs and Susceptibility to Mycobacterial Diseases
Evaluation of PIIDs with increased susceptibility to BCG infections

- MSMD deficiencies
  - Receptors’ expression (IFNγRC and IL-12/IL-23RC)
  - IFNγRC signaling (early and late steps, STAT1 phosphorylation and MHC-II up-regulation) and IL-12RC signaling (early and late steps, STAT4 phosphorylation and IFNγ up-regulation)
  - NFκB signaling
  - IL-12p70 or p40 detection
  - gDNA/cDNA sequencing
BCG in Primary Immunodeficiencies

IFNγR1 DP deficiency

IFNγR2 AR deficiency

IFNγR1 AR deficiency
BCG in Primary Immunodeficiencies

IL-12Rβ1 deficiency
BCG in Primary Immunodeficiencies

IL-12Rβ1 deficiency
BCG in Primary Immunodeficiencies

Treatment of PIDs with increased susceptibility to BCG infections

- Specific (based on germ sensitivity)
- Prolonged
- Multidrug (parenteral treatment should be considered)
- Adjuvant treatment with IFNγ in patients with preserved IFNγ signaling (partial IFNγR1 and IFNγR2 deficiencies, dominant STAT1 deficiency, IL-12Rβ1 deficiency, IL-12p40 deficiency and NEMO)...IFNα adjuvant treatment?
- Prophylactic
BCG in Primary Immunodeficiencies

CGD Pulmonary TB

CGD Localized BCGitis
BCG in Primary Immunodeficiencies

T-/B-/NK-
Artemis

T-/B-/NK-
ADA
BCG in Primary Immunodeficiencies

T-/B-/NK- ADA
Immune reconstitution post Peg-ADA
BCG in Primary Immunodeficiencies

Principles & Conclusions

- Do not harm
- Diagnosis (clinical, flow, functional, genetic)
- Treatment
- Prophylaxis
BCG infection in SCID patients

Post-vaccinal BCG infection in SCID patients/International survey

Diagnosis and treatment policies

Dr. Nima Rezaei (Iran), Dr. Graham Davies (UK), and Dr. Benedicte Neven (France)

BCG infection in SCID patients is a devastating complication affecting most SCID patients born away from Europe, North America, and Australia. Lack of standardization and information regarding diagnosis, treatment, risk factors, and outcome makes difficult the management of this preventable complication.

Questionnaire: Two pages Excel-based International Survey sponsored by different International Societies (ESID, CIS, LASID, Jeffrey Modell Foundation, …)

Where to get the Survey and Contact Information

BCG infection in SCID patients

Immunization coverage with BCG at birth, 2006

28 centers from 17 countries represented (Argentina -3-, Brazil -3-, Colombia, C. Rica, Czech Republic, Egypt, France, Iran, Japan -4-, Kuwait, Mexico -2-, Oman, Poland, Portugal, Russia, Turkey -3-, and UK -2-)
BCG infection in SCID patients

Post-vaccinal BCG infection in SCID patients/
International survey

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Where to get the Survey and Contact Information


INCIDENCE  VACCINE  PATIENT  INTERVENTION
Results

Demographic data

<table>
<thead>
<tr>
<th>Country (centers)*</th>
<th>Universal BCG vaccination at birth†</th>
<th>BCG-vaccinated patients with SCID (n = 349)</th>
<th>HSCT† (n = 190)</th>
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<tbody>
<tr>
<td>Argentina (3)</td>
<td>Yes</td>
<td>10</td>
<td>6</td>
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<tr>
<td>Brazil (3)</td>
<td>Yes</td>
<td>58</td>
<td>24</td>
</tr>
<tr>
<td>Colombia (1)</td>
<td>Yes</td>
<td>6</td>
<td>1</td>
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<tr>
<td>Costa Rica (1)</td>
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<td>10</td>
<td>6</td>
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<tr>
<td>Czech Republic (1)§</td>
<td>Yes</td>
<td>15</td>
<td>8</td>
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<td>Egypt (1)</td>
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<td>France (1)</td>
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<td>Iran (1)</td>
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<tr>
<td>Japan (4)</td>
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<td>6</td>
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<tr>
<td>Kuwait (1)</td>
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<td>4</td>
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<td>Poland (1)</td>
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<td>5</td>
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<td>Portugal (1)</td>
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<td>5</td>
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<td>Russia (1)</td>
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<td>0</td>
</tr>
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<td>Turkey (3)</td>
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<td>27</td>
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<tr>
<td>United Kingdom (2)</td>
<td>No</td>
<td>54</td>
<td>46</td>
</tr>
</tbody>
</table>

1Out of 821 SCID patients diagnosed at the collaborating centers, 349 were BCG-vaccinated
### Results

<table>
<thead>
<tr>
<th>BCG Complications</th>
<th>Localized Regional</th>
<th>Localized Extra regional</th>
<th>Disseminated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>~1/2,500</td>
<td>~1/10,000</td>
<td>~1/100,000</td>
</tr>
</tbody>
</table>

**Incidence**

- **BCG Complications**
  - Localized: ~1/2,500
  - Localized Extra regional: ~1/10,000
  - Disseminated: ~1/100,000

![Image: BCG complications](image)

Bull Int Union Tuberc 1988, 63:47-59
Results

<table>
<thead>
<tr>
<th>BCG Complications</th>
<th>Localized</th>
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</table>

BCG Complications

- Localized: 0%
- Regional: 0%
- Extra regional: 100%
- Disseminated: 100%

SCID-BCG Manifestations

- Localized: 49%
- Disseminated: 34%
- No Manifestations: 17%

- Localized: X 33,000 increase
- Disseminated: X 400 increase

Bull Int Union Tuberc 1988, 63:47-59
Results

SCID-BCG Manifestations

- 49% No Manifestations
- 34% Localized
- 17% Disseminated

VACCINE

BCG strain and Manifestations

- Danish: 80 (No manifestations) 20 (Localized) 0 (Disseminated)
- Moreau: 60 (No manifestations) 30 (Localized) 0 (Disseminated)
- Pasteur: 20 (No manifestations) 30 (Localized) 10 (Disseminated)
- Glaxo: 20 (No manifestations) 0 (Localized) 0 (Disseminated)
- Tokyo: 10 (No manifestations) 0 (Localized) 0 (Disseminated)
- Russia: 10 (No manifestations) 0 (Localized) 0 (Disseminated)

BCG vaccination technique

- Deltoid
  - 349 SubQ
  - 303 Intradermal
- Route of administration

None of the BCG strains showed dissemination.
Results

Type of SCID

- Gamma-c: 54%
- ADA: 10%
- IL-7Ra: 7%
- MHC-II: 5%
- Zap-70: 6%
- RAG1-2: 10%
- Artemis: 1%
- PNP: 1%
- Jak3: 3%
- Other: 2%
- Not Defined: 1%

Age at SCID diagnosis

- > 12 m: 10%
- 7-12 m: 54%
- 4-6 m: 10%
- > 1-3 m: 10%
- ≤ 1 m: 6%

PATIENT
Results

Type of SCID

- Gamma-c: 54%
- ADA: 7%
- IL-7Ra: 5%
- MHC-II: 6%
- Zap-70: 1%
- RAG1-2: 2%
- Artemis: 1%
- PNP: 3%
- Jak3: 1%
- Other: 1%
- Not Defined: 1%

BCG Manifestations

- IL2RG
- RAG1/RAG2
- ADA
- MHC-II
- IL7RA
- Artemis
- JAK3
- PNP
- ZAP-70
- Cernunnos

- No Manifestations
- Localized
- Disseminated
### Results

#### SCID-BCG Manifestations
- **Localized:** 17%
- **Disseminated:** 34%
- **No Manifestations:** 49%

#### Age at BCG Manifestations
- **≤ 1 m:**
  - Localized: 0
  - Disseminated: 10
- **1-3 m:**
  - Localized: 20
  - Disseminated: 40
- **4-6 m:**
  - Localized: 30
  - Disseminated: 60
- **> 6 m:**
  - Localized: 40
  - Disseminated: 70

#### Site at BCG Diss. Manifestations
- **Lymph nodes:** Localized: 0, Disseminated: 50
- **Skin:** Localized: 0, Disseminated: 60
- **Lung:** Localized: 10, Disseminated: 50
- **Liver:** Localized: 20, Disseminated: 40
- **Bone marrow:** Localized: 30, Disseminated: 30
- **Bone:** Localized: 40, Disseminated: 20
- **Spleen:** Localized: 50, Disseminated: 10
- **Soft tissue:** Localized: 60, Disseminated: 0
- **Gastrointestinal tract:** Localized: 70, Disseminated: 0
- **Genitourinary tract:** Localized: 80, Disseminated: 0
- **Blood:** Localized: 90, Disseminated: 10
Results

SCID-BCG Manifestations

- Localized: 17%
- Disseminated: 34%
- No Manifestations: 49%

**Median lymphocytes at SCID diagnosis**

<table>
<thead>
<tr>
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<th>No manifestations</th>
<th>Localized or disseminated</th>
</tr>
</thead>
<tbody>
<tr>
<td>T cells/μL (25th-75th percentile)</td>
<td>197 (14-942)</td>
<td>49 (5-343)</td>
</tr>
<tr>
<td>B cells/μL (25th-75th percentile)</td>
<td>103 (5-640)</td>
<td>140 (11-710)</td>
</tr>
<tr>
<td>NK cells/μL (25th-75th percentile)</td>
<td>160 (38-410)</td>
<td>100 (19-366)</td>
</tr>
</tbody>
</table>

<250 T cell/μL at SCID dx

2.1 X risk of developing BCG complications (95% CI 1.4-3.4)
## Results

### SCID-BCG Manifestations

<table>
<thead>
<tr>
<th></th>
<th>BCG vaccination at ≤1 mo</th>
<th>BCG vaccination at &gt;1 mo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>88 (34.8)</td>
<td>40 (46)</td>
<td>NS</td>
</tr>
<tr>
<td>Male</td>
<td>165 (65.2)</td>
<td>47 (54)</td>
<td></td>
</tr>
<tr>
<td><strong>Age at SCID diagnosis (mo), median (range)</strong></td>
<td>5 (0.5-48)</td>
<td>6 (0.5-100)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>BCG-associated complications, no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No manifestations</td>
<td>115 (44.6)</td>
<td>54 (62.1)</td>
<td>.006</td>
</tr>
<tr>
<td>Loc/Diss manifest</td>
<td>143 (55.4)</td>
<td>33 (37.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Age at HSCT (mo), median (range)</strong></td>
<td>7 (0.5-75)</td>
<td>8 (0.5-107)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Mortality in BCG-SCID</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCG-rel, no. (%)</td>
<td>45 (18)</td>
<td>0 (0)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Overall, no. (%)</td>
<td>132 (52.8)</td>
<td>38 (43.7)</td>
<td>NS</td>
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</table>
Results

Table: Antimycobacterial treatment in HSCT patients

<table>
<thead>
<tr>
<th>Antimycobacterial treatment in HSCT patients</th>
<th>BCG asymptomatic</th>
<th>BCG Symptomatic</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG-associated complications, no. (%)</td>
<td>2/64 (3)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>BCG-related deaths, no. (%)</td>
<td>0/64 (0)</td>
<td>7/120 (6)</td>
<td>0.09*</td>
</tr>
<tr>
<td>IRS (n=55 patients)</td>
<td>5/64 (8)</td>
<td>50/126 (40)</td>
<td>0.001</td>
</tr>
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*0.04, one sided

Pie chart: SCID-BCG Manifestations
- Localized: 17%
- Disseminated: 34%
- No Manifestations: 49%
Preliminary Results

**SCID Treatment**
- Matched Related (n=50)
- Matched Unrelated (n=33)
- MisM Related (n=31)
- MisM Unrelated (n=12)
- Gene Ther (n=3)
- Other (n=2)
- No specific treatment (n=189)

**Time from vaccination to death due to BCG complications**

**Time from vaccination to death before HSCT**

**Time from HSCT to death after HSCT**

- p < 0.0001
- p = 0.01
- p = 0.96

Time since vaccination (months)

Time since vaccination (months)

Time since transplant (months)
Conclusions

- SCID patients are highly susceptible to BCG complications and their presence associates with poor outcome and mortality

- Factors related to the vaccine itself (strain), vaccination route (intradermal), or SCID type do not appear to be associated with BCG complications

- Number of T cells at SCID diagnosis are inversely associated with BCG complications

- Age at BCG vaccination appears as a critical variable associated with BCG complications in SCID patients

- Pre-symptomatic antimycobacterial treatment (scheme, route, and duration to be defined) might be related to favorable outcomes

- HSCT significantly reduces mortality even among the most severe BCG complications
Conclusions

- Delaying BCG vaccination until after 1 month of age should diminish BCG-associated complications in patients with SCID and should not adversely affect BCG preventable disease.
Acknowledgments

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Patients and their families