Immune deficiency and vaccinations

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Vaccination of immuno-deficient patients

Challenge with two aims:

- To protect against preventable infectious diseases as performed for immuno-competent individuals
- To compensate some defective pathway of immune responses

  e.g. - splenectomized patients
        - complement deficiency
Vaccination of immuno-deficient patients

- Not easy to adapt vaccine schedules to immuno-compromised subjects
  - Biomarkers of vaccine protection?
  - Mechanism of immunosuppression
    - illness / drugs
    - immaturity / immuno-senescence

- But we have to do it....
Biomarkers for vaccine efficacy

< adaptative immune responses

➢ Humoral immune responses: ANTIBODIES

  • Amount: what?
  • Quality: affinity –how and which?
    infants/elderly: adequate IgG Ab concentrations but reduced opsonophagocytic activity (low Ab affinity)
  • Memory – how? Abs versus memory B cells

➢ CELLULAR IMMUNITY: T lymphocytes

  • Amount: Cytokines
    Cytotoxic T lymphocytes
  • Quality: multi-functionnal T cells
  • Memory
Mechanisms of immunosuppression

- Removal of lymphoid organs: stem cell transplantation – splenectomy
- Extreme of age: infancy / elderly
- Chronic renal failure
- Transplantation
- Immunosuppressive drugs
- Infection
To understand the mechanisms of immune suppression and their impact on vaccine efficacy, it is important to remember by which mechanisms antibodies are synthesized.
ANTIBODIES

PLASMATOCYTES

B LYMPHOCYTES

Blood

Mucosal Effector sites

Bone marrow

Naive B lymphocytes:
- Follicular B cells: IgM+ IgD+
- Marginal zone B cells: IgM+ CD21+
- Immature B cells: IgM+ CD5+

Memory B lymphocytes

Lymph nodes

Spleen

Mucosal Inductive sites

Spleen

Fetal Liver

Bone marrow
Immature B cells

- IgM+ CD20+ CD27+ CD43+ CD5+/-
- At least partially colonise mucosal surfaces
- Spontaneous production of « natural Abs »
  >> polysaccharides/ auto-Ags (anti-A / anti-B) / LPS...
  → 1st line of defence >> bacterial and viral pathogens
      innate immunity
- Majority of the B lymphocytes at birth
  Diminution thereafter
  Very low number in elderly

Marginal zone B cells

**Spleen:**

- **Red pulp:** - important filter for the blood (macrophages)
  - removing microbes and damaged cells

- **White pulp:** - lymphocytes organised around an arteriole
  - initiation of adaptative immune responses >> blood-borne antigens

- **Marginal zone:** - interface between the red and the white pulp
Marginal zone B cells

- Phenotype: IgM and IgD are the only surface Ig expressed. CD21 (CR2 – C3d receptor) is a phenotypic marker.

- The spleen is need for:
  - their generation
  - their survival

- B cells with a limited repertoire of antigen specificities: polysaccharides - glycolipids – nucleic acids -
  - S. pneumoniae
  - Neisseiria meningitidis
  - Haemophilus influenzae type b
Marginal zone B cells

- Initiation of the Ab response \( \leftrightarrow \) polysaccharidic antigens

- B cells activated by multivalent antigens (repeated identical antigenic epitopes) \( \rightarrow \) cross-linking of the BCR

- Co-stimulation by activation of CR2/CD21 (C3b receptor \( \leftarrow \) alternative pathway activation by microbes) and/or TLR (PAMP from microbes)

- No need for T cell help

**IgM memory B cells** (CD27+IgM+) and **short-lived IgM plasma cells**

1st line of defense \( \leftrightarrow \) encapsulated organisms (effector natural B cells)

- Help provided by a subpopulation of neutrophils (extracellular nets) \( \rightarrow \) IgG and IgA class switching may occur with enhancement of somatic hypermutation and plasmablast differentiation
Marginal zone B cells

- Low numbers:
  - Children < 2 yrs
  - Elderly
  - Splenectomized persons
  - Hyposplenic states
  - A subgroup of common variable immunodeficiency

- Poor initiation of the Ab response >> polysacharidic antigens

- Functional impairment (isotype switching)
  - Neutropenia
Splenectomy / Hyposplenic states

• Absence of phagocytic filter

• Lack of opsonins produced by the spleen (tuftsine – properdin)
  – Absence of IgM memory B cells
    – Absence of natural Abs
    – No initiation of anti-polysaccharide Ab response
    – Poor opsonisation of encapsulated bacteria
      • Poor elimination by the liver
Follicular B cells

- Activated by T cell dependent antigens in the spleen / lymph nodes

Short-lived plasma cells

B cells going back to the follicles for further maturation
Maturation of the follicular B lymphocyte in the germinal center

1) **Isotype switching**: switched memory B cells (CD27+ IgM-)
   - T cell interactions required: CD40 engagement (B: CD40L)
   - activation of the enzyme *activation-induced deaminase* (AID)

- follicular helper T cells – CXCR5+ - IL-21+ - ICOS+

- the specific Ig heavy chain is selected by cytokines produced by the helper T cells activated by microbes
Maturation of the follicular B lymphocyte in the germinal center

2) Affinity maturation:
   T cell dependent somatic mutation of Ig genes
       (increasing stimulations → increasing numbers of mutations)
   and
   selective survival of B cells producing Abs with the highest affinities
Primary and secondary antibody responses
Removal of primary lymphoid organs

• Splenectomy

• Hematopoietic stem cell transplantation
  - Protective immunity induced by vaccines administrated during childhood is lost
  - Immune reconstitution occurs within several months after autologous HSCT but takes up to a year after allogeneic HSCT
  - Vaccination post HSCT does not ensure complete serological response (especially if GVHD)
  - Response to PS vaccines remains poor but good response to the conjugate PS vaccine (vaccine 3 months after HSCT – Ab response 1 month after 3rd dose (Cordonnier C Bone marrow Transplant 2010)
  - Vaccination should start 6 months after HSCT (no live vaccines)
Extreme ages: infants/ elderly

1) Infants

- Infants are able to produce Abs >> proteic Ags but not >> PS Ags (low IgM memory B cells)

- Quality of the Ab response? Avidity
- Quality of the cellular immune response?


*Functional deficits of pertussis-specific CD4+ T cells in infants compared to adults following DTaP vaccination.*

*Sharma SK, Pichichero ME.*

- Duration of memory immune responses?
- Role of maternal antibodies: protection/ interference
2) Ageing

- Ageing affects both the humoral and the cellular immune responses

- Humoral immunity is affected both quantitatively and qualitatively
  - Both subsets of B cells involved in Ab response $<\!\!<$ PS are decreased
    - Less production of IgM Abs (PS) / young adults
      (earlier production and better opsonizing activity)
  
  - Less Ig diversity / loss of oligoclonality of the Ab response

  - Decreased ability to produce high affinity protective Abs
    $<\!\!<$ Intrinsic B cell defects (decreased AID...)
    and
    $<\!\!<$ T cell defects (signal transduction defects)

  - Reduction of the duration of the Ab response
2) Ageing

- Search for biomarker of human B cell function to predict vaccine effectiveness

- The % of switched memory B cells before vaccination is correlated with the serum Ab response to the pandemic \textit{H1N1 vaccine} (hemagglutination inhibition response)

-> May be useful to identify individuals at risk of poor response

Chronic renal failure

- Serologic response to vaccination is impaired
- Antigen-specific effector memory CD4+ T cells are severely depressed

- Reactogenicity to hepatitis B vaccine is impaired – the immunogenicity should be improved
- Even the response to TT is depressed
- Poor response to Influenza
- Relatively good response to PS
- Good Ab response to Haemophilus influenzae type b
Organ transplantation

The immunogenicity of vaccines is variable depending of:
- The type of transplant
- The time from transplant:
  normal responses if vaccination after ~ 6 months (influenza)
- The immunosuppressive regimen
- The study endpoint (seroprotection/ seroconversion/ other...)

Overall...

Transplant recipients do mount a humoral immune response but
- the level of protection is usually reduced
- immunity is waining quite rapidly
Kidney transplantation

- Almost normal Ab production >> PS early after the vaccination in stable condition
- Short half life of the Abs

Panel 1: tetanus anatoxin Ab levels during the first year after renal transplantation
- Half life 7.7 months

Panel 2: Pneumococcal polysaccharid Ab levels during the first year after renal transplantation
- Half life ~ 10 months

- Poor Ab response to Influenza

<table>
<thead>
<tr>
<th>GMT (95% CI)</th>
<th>RT Patients (n = 111)</th>
<th>HD Patients (n = 53)</th>
<th>Controls (n = 21)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMT day 0</td>
<td>11 (8 to 14)</td>
<td>8 (6 to 11)</td>
<td>9 (4 to 19)</td>
<td>0.56</td>
</tr>
<tr>
<td>GMT day 30</td>
<td>50 (34 to 72)</td>
<td>77 (44 to 136)</td>
<td>361 (166 to 782)</td>
<td>&lt;0.001&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>GMT ratio</td>
<td>5 (3 to 6)</td>
<td>9 (5 to 16)</td>
<td>38 (19 to 78)</td>
<td>&lt;0.001&lt;sup&gt;a,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Seroconversion (%)</td>
<td>49/111 (44%)</td>
<td>30/53 (57%)</td>
<td>19/21 (90%)</td>
<td>&lt;0.001&lt;sup&gt;a,d&lt;/sup&gt;</td>
</tr>
</tbody>
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Organ transplantation

**General recommendations** (Abuali MM et al, Pediatric Transplantation 2011)

- As many immunizations as possible should be administered PRIOR to transplantation as the exact effect of immunosuppression on the immune response to vaccines is not completely understood.

- Antibodies to vaccine preventable diseases should be measured as part of pretransplant screening protocols.

- As the post-transplantation immunity wanes for some partially unknown reason, antibodies should be measured to evaluate patients for waining immunity and appropriate boosters should be administered.
Immunosuppressive treatments: 
1) Corticoïds

• Monocytes/ macrophages:
  – Lower number of circulating cells
  – Lower expression of MHC class II molecules and Fc receptors
  – Lower synthesis of cytokines and prostaglandins

• T cells:
  • Lower number of circulating cells
  • Lower production and action of IL-2
    • Lower T cell proliferation
    • Lower B cell dependent Ab production

- Good Ab level after Pn PS vaccine in patients treated with 10-35 mg prednisolone /day (Lahood N, Ann Allergy 1993)
- Variable response to a seasonal influenza vaccine in LED patients treated with 10.8 + 5.9 mg glucocorticoids/day (Wallin L Acta Reumatol 2009)

Live attenuated vaccines are contra-indicated (> 20 mg/day prednisone) Wait at least 4 weeks after discontinuing high dose steroid treatment
Immunosuppressive treatments:
2) targeting the B cells

Role in the amplification of de novo B cell response

CD20 not expressed on Ab-producing cells
No effect on Ab secretion

Vincenti F Am J Transplant 2008
Immunosuppressive treatments: 2) targeting the T cells
THANKS YOU
for your attention