Infection Prophylaxis Including Vaccination

For the Consensus Panel 1

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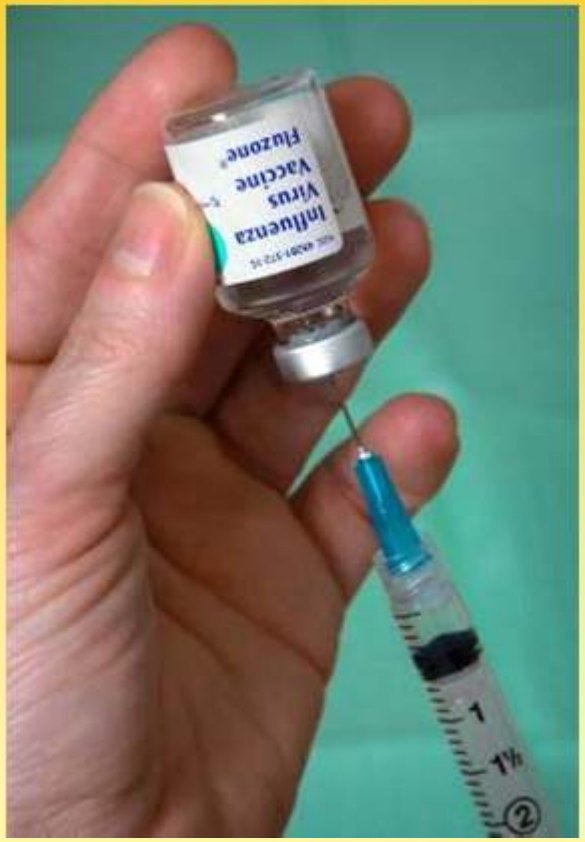
Infection Prophylaxis including Vaccination for MM Patients

Outline

1. **Vaccines**
   1. Key points
   2. Which vaccines; when to vaccinate; Vaccinate close contacts.
   3. Assessing response to vaccination.
   4. Travel vaccines.
2. **Immunoglobulin replacement**
   1. Potential candidates
   2. Optimal dosage-schedule; Duration of therapy
   3. Route of administration; post exposure prophylaxis (VZV)
3. **Antimicrobial prophylaxis**
   1. Risk stratification
   2. Antimicrobial agents
4. **Other preventive methods**



Indications for vaccination in multiple myeloma

Indications for Vaccination in MM
Key Points

1. Efficacy:
   - Limited but one can take advantage of partial protection.
   - Vaccination of close contacts strongly recommended .
2. Gaps in knowledge:
   - Very few studies in MM patients /None with the novel agents.
   - Trials with clinical endpoint (i.e. infections) lacking.
   - No efficacy data for influenza virus vaccine (live).
   - No safety data for influenza (live), varicella, zoster vaccines.

Key Points

Avoid Live Vaccines

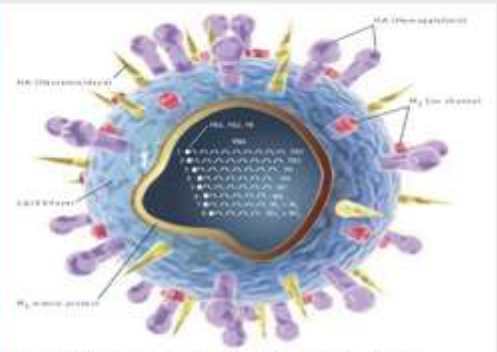
-Influenza (intranasal)
-MMR
-Varicella
-Zoster
-Polio (oral) [alternative]
-BCG
-Yellow fever

Unless

-MGUS, Smoldering or
- Remission *and*
> 6 mos after end chemo

Inactivated = Safe

Influenza virus



WHICH VACCINE?

Streptococcus pneumoniae

23-valent polysaccharide (PPSV23)[1]

13-valent conjugate (PCV13)

Antibiotics

1. MMWR 1997;46(RR-8)
2. MMWR 2000;49(RR-10
3. www.cdc.gov

- Risk factors for invasive disease:
  - Defects in humoral immunity
  - Immunosuppressive therapies
  - Renal failure / nephrotic syndrome
  - Asplenia, DM, COPD, CHF

- PPSV23 recommended by the CDC.
  Repeat in 3 -5 years.
- Alternative strategy:
  3 doses of PCV 13 + 1 dose PPSV23 at 12 months to broaden immune response or a 4th PCV dose if severe immunocompromise

- If infection despite vaccination, use antibiotic prophylaxis based on local epidemiology: penicillin or fluoroquinolone.

WHICH VACCINE?

2010-11 Influenza Vaccine

High-Dose Inactivated Influenza Vaccine for ≥65 Years[1]

1.MMWR; 59(16);485-86, 2010.

2.Keitel, W. A. et al. *Arch Intern Med*; 166 (10): 1121-7, 2006.

3.Falsey A. et al. *J Infect Dis.* 200: 172-180, 2009

2010-2011: only 1 vaccine, not 2.

- Vaccine strains:
  - Same A/California/7/2009-like H1N1
  - New A. H3N2 strain for North Hemisphere
  - B. was in 2009-10 seasonal vaccine
- All 3 worldwide this season.

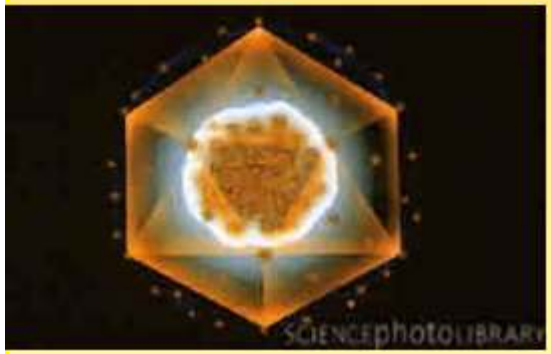
HD-fluzone (Sanofi-Pasteur):

- Increased x 4 amount of viral antigen vs. other TIVs[1,2]
- Up to 80% higher antibody titers to Flu A vaccine strains vs. standard-dose for ≥65 y.o. +/- underlying medical conditions[2]

Antiviral prophylaxis may be needed

WHICH VACCINE?

Hepatitis B Recombinant Vaccine



1. HBsAg (+) close contacts.
2. Travel to areas of high endemicity.
3. Behavioral/occupational exposure.
4. Chronic liver / renal disease.

1. May test ≥ 1 month after last dose, then every 6-12 mos.

2. Consider revaccinating nonresponders, preferably after the cause for non-responsiveness has resolved.
3. Booster if titer falls to <10 IU/L.
4. May retest every 4-5 years.

WHEN TO VACCINATE?

No Perfect Timing!

1. **INDIVIDUALIZE**
   - Risks / benefit assessment
     - Individual's susceptibility to infection
     - Institution / country guidelines.
2. **ASAP** (MGUS, smoldering myeloma).
3. **For patients scheduled for chemo**
   - ≤ 14 days before initiation of chemo
   - Before stem cell mobilization
   - 6 months after completion of chemo
   - 6-12 months after Auto-Transplant
   - Upon achievement of best response
4. **Useful?**Lymph/CD4, uninvolved s-Igs

VACCINATE CLOSE CONTACTS

Live vaccines

- Avoid direct contact with patients for 4- 6 weeks after vaccines.
- But individualize (personal condition, institution/country guidelines) .

1. **All non-immune close contacts:**
   - *Influenza* (+healthcare workers)
2. **Only those at risk:**
   - *Hepatitis A :* travel to areas of high endemicity, behavioral and occupational exposure, chronic liver disease
   - *Hepatitis B:* same + ESRD/hemodialysis
   - *Polio*
   - *Tetanus, diphtheria, pertussis*
   - *Meningococcus* : younger & military.
1. Live vaccines for close contacts:
   - MMR :> 1 y.o., not pregnant or Immunosupp.
   - Varicella : same + negative/uncertain H/O varicella and negative serostatus.

Assessing Serologic Response

1. Surrogate marker for protection (level and/or duration).
2. Relatively simple and inexpensive for Hep. B and tetanus.
3. May not be feasible for others b/o several limitations:
   - Large technical variability, costs, availability.
   - Serologic response to a polysaccharide (PS) Ag. does not imply responsiveness to all PS Ags. Same for protein Ags.
   - Evaluation of responsiveness to *S. pneumoniae*: measure ≥ 14 serotypes to pneumo. PSs (but titers to serotypes conjugate vaccine not relevant to PS responsiveness).

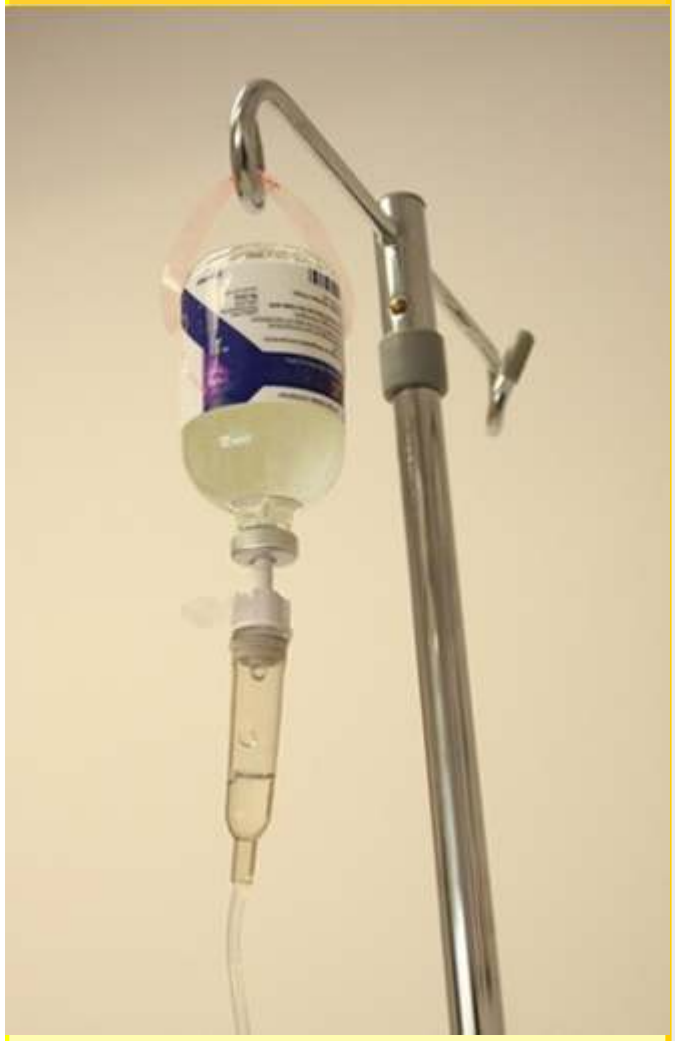
Travel Vaccines
Based on Host and Travel Itinerary

Vaccine performance	Vaccine type	Risk
Effective and safe	Influenza § , HBV♂, HAV☼, polio (inactive)☼, rabies, meningococcus, Japanese encephalitis	Endemic, other
Effective, Not safe (live)	~~Yellow fever~~	Endemic
Moderately effective, Not safe (live)	~~BCG~~, ~~Typhoid (oral)~~ ☼	Endemic, other

§ Travel to southern hemisphere (April -Sept.); ☼food/water; ♂STD

Data re: **safety / efficacy** of some vaccines in ICH lacking.

IVIG/SCIG: when vaccination contraindicated or insufficient time to develop immunity, IVIG/SCIG may provide protection against measles, mumps, rubella, hep. A/B, varicella, rabies.



Immunoglobulin Replacement to Prevent Infections in Patients with Myeloma

IMMUNOGLOBULIN REPLACEMENT

Gaps in knowledge

Potential candidates

Against IVIG:

- Gaps in knowledge
- Cost
- Effective antibiotics
- Renal toxicity

Gaps in knowledge:

- IVIG prevented serious infection during the plateau phase of myeloma. However, no antibiotic prophylaxis, and mildly immunosuppressive chemo.
- No level of s-Ig shown protective.
- No data exist to support their role with novel agents or the optimal dosage-schedule/duration of therapy.

Selected candidates:

- Significant hypogammaglobulinemia +
- Serious infections despite vaccination & antimicrobial prophylaxis +
- Infection likely to respond to IVIG

IMMUNOGLOBULIN REPLACEMENT

Dosage – schedule

Duration of therapy

1. **Optimal dosage-schedule:**
   - Gaps in knowledge
   - Dose schedule which keeps patient free from serious infections.
   - Trough IgG level > 400 mg/dL?
     - Not practical; IgG MM; ↑ excessive use

1. **Duration of therapy:**
   1. Gaps in knowledge
   2. INDIVIDUALIZE:
      1. Risks / benefits
      2. Lymphocyte/CD4, uninvolved s-Ig, remission status, ongoing immunosuppressive therapies.
   3. A 6 mo trial then stop & assess rate of serious infections.

IMMUNOGLOBULIN REPLACEMENT

Routes:

Intravenous

Subcutaneous

- **Premedicate**

-Acetaminophen

-Diphenhydramine

-Glucocorticoids

- **Hydrate**
- **Slow rate**
- **Monitor**

- INTRAVENOUS (IVIG):
  - Half-life ~ 3 weeks
  - 1-10 days in HSCT pts, fever, infection.
  - Well tolerated /rate-related reactions
  - Acute renal failure (sucrose-containing)
  - IgA-depleted if congenital deficiency
  - Local IVIG products recommended.
- SUBCUTANEOUS (SCIG) :
  - As effective as IVIG for infection
  - Fewer systemic reactions/tolerated by most pts with reactions to IVIG.
  - Safe in most IgA-deficient pts.
  - Convenient (self-infuse/ no IV access)
  - More consistent s-IgG levels

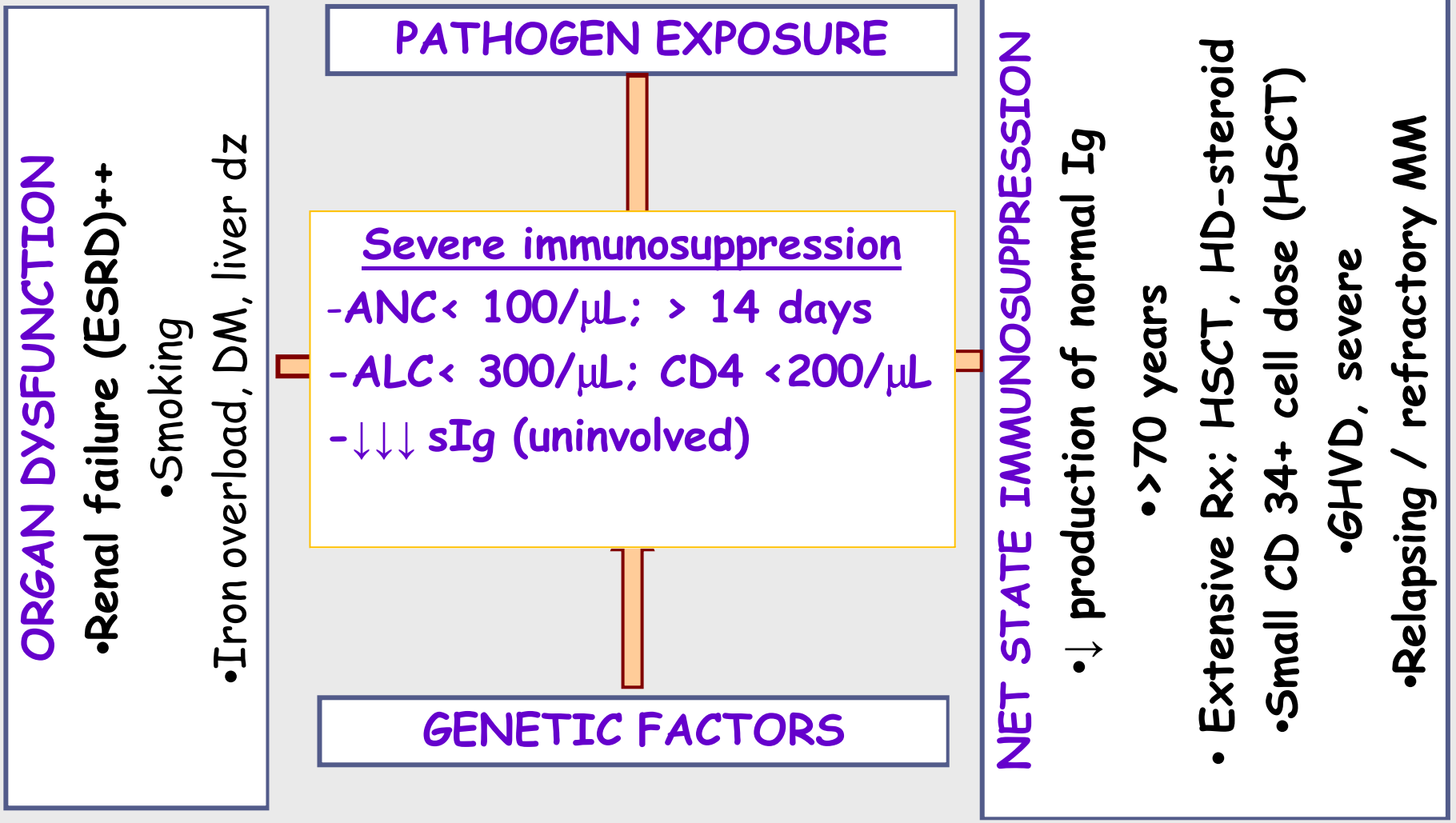
Post Exposure Prophylaxis for Varicella/Zoster

1. Determine the risk following exposure:
    1. **Pt susceptible?** (bortezomib, no vaccination & no H/O varicella) All immunocompromised pts with H/O varicella can be considered immune, except HSCT recipients.
    2. **Exposure significant** enough to result in infection ? (prolonged face-to-face or close indoor contact ≥ 1 h)
    3. **Higher risk for complications** (severe immunosuppression)?

2. Post-exposure prophylaxis:
    1. Varicella/Zoster
        1. Acyclovir
        2. VariZIG IM within 96 h or 1 dose of IVIG (400 mg/kg)
    2. Hepatitis A / B

Infection Prophylaxis in Patients with Myeloma

Infection Prophylaxis
Risk Stratification



Prophylactic Regimens of Antimicrobial Agents

1. **Bacterial infections:**
   - Neutropenic:
     1. levofloxacin
   - Non-neutropenic:
     1. TMP/SMX or amoxicillin
2. **Fungal infections:**
   1. **Oral thrush:** Fluconazole/clotrimazole
   2. ***P. jiroveci*:** Bactrim or dapsone
3. **Viral infections:**
   1. **HSV/VZV:** acyclovir or valacyclovir
   2. **Influenza viruses:**
      1. Neuraminidase inhibitors (if high-risk)

Preventive Measures in Severely Immunosuppressed MM Patients

1. **Maintain good personal hygiene**
   1. Handwashing
   2. Good dental hygiene
   3. Protected sexual encounters
2. **Avoid at risk environmental exposure**
   1. Infected individuals (suspected or confirmed infection)
   2. Outdoor activities that pose risk for infections
   3. Public swimming pools
3. **Take special precautions**
   1. Food/water
   2. Pets
   3. Travel

Food & water

Bloodborne & STD

TRAVEL PRECAUTIONS

Vectors

Animals

Infection Prophylaxis including Vaccination
Conclusions

1. **Vaccination:**
   1. Which ones? *S. pneumonia*, Influenza and HBV
   2. When? individualize but ASAP
   3. Vaccinate close contacts
   4. Travel vaccines as appropriate
2. **Ig replacement**
   1. Selected patients
   2. Individualize dose-schedules/ duration of therapy
   3. IV or SC routes
3. **Prophylaxis**
   1. Assess risk for infection
   2. Antimicrobial regimens
4. **Other preventive measures** (including for travel)

THANK YOU

Therapies for Multiple Myeloma and their Impact on the Immune System

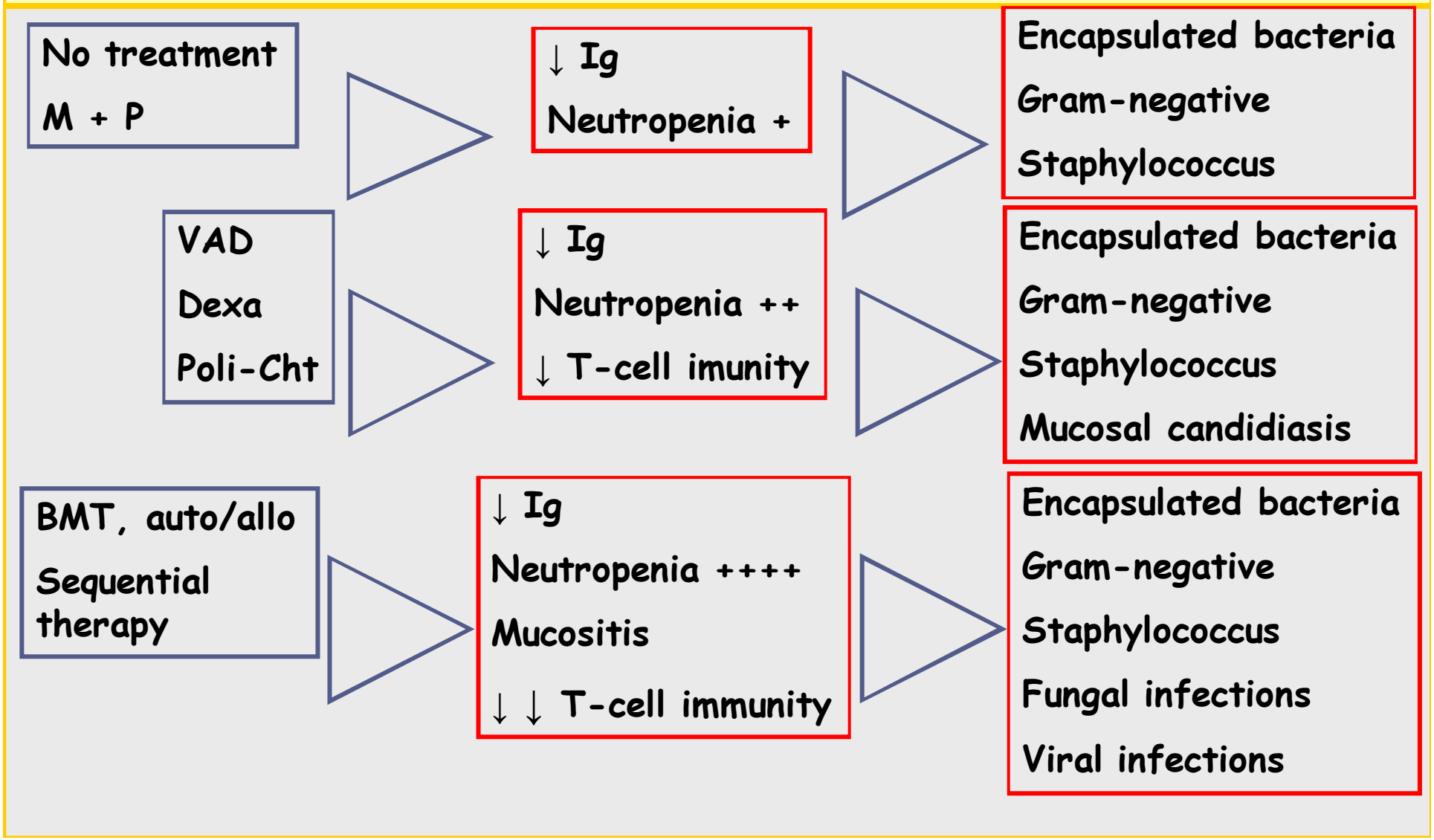
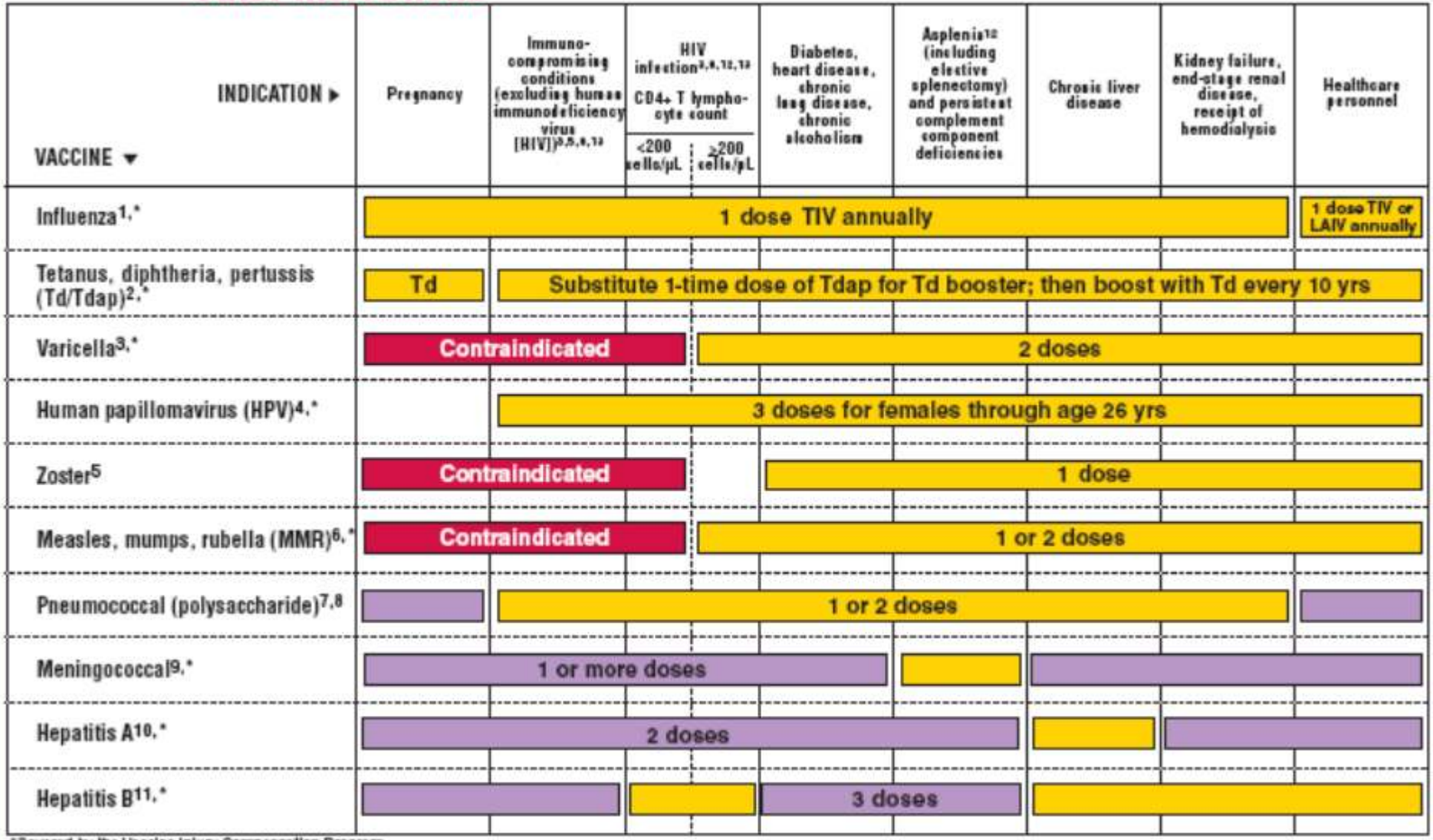


Figure 2. Vaccines that might be indicated for adults based on medical and other indications



*Covered by the Vaccine Injury Compensation Program.

For all persons in this category who meet the age requirements and who lack evidence of immunity (e.g., lack documentation of vaccination or have no evidence of previous infection)

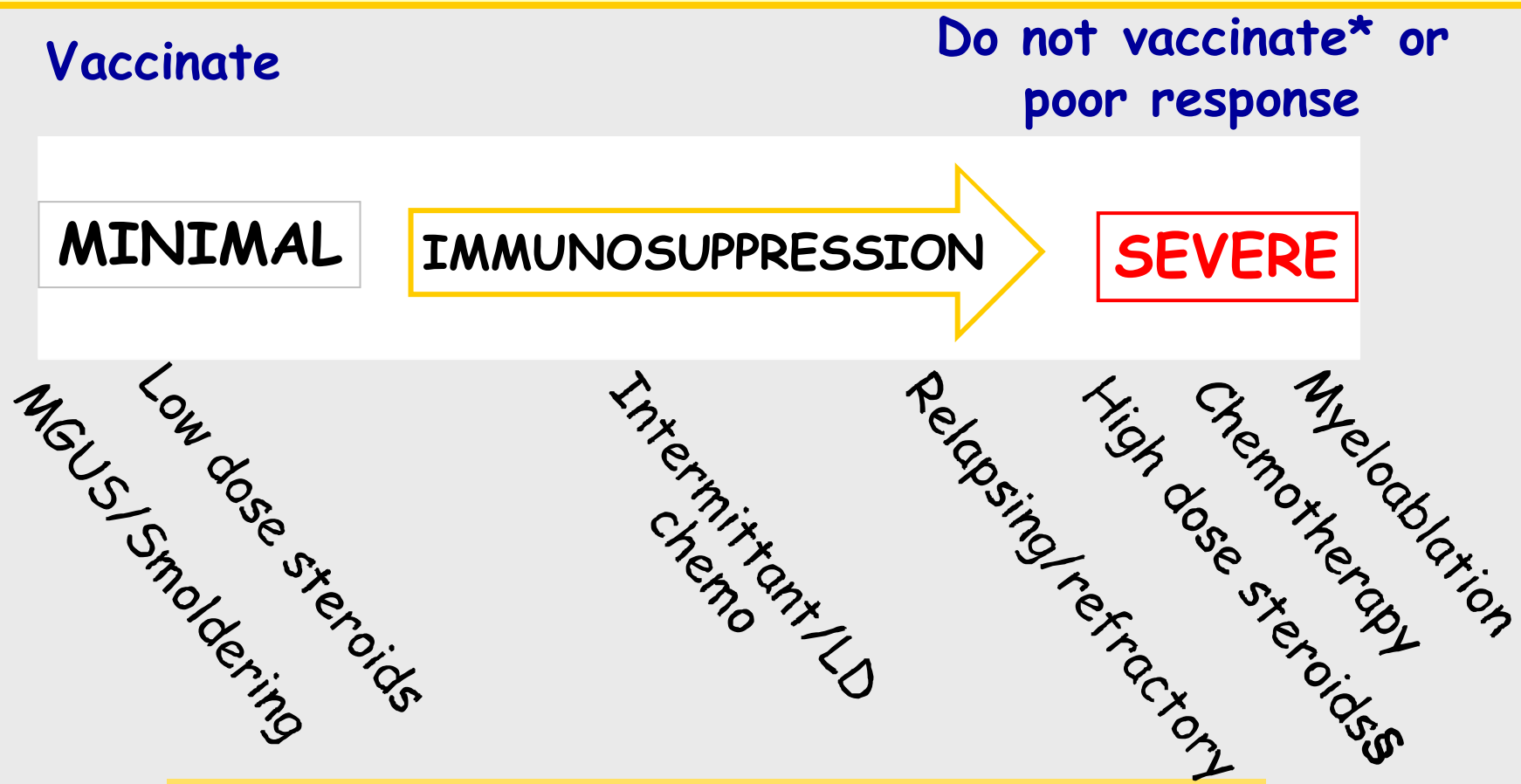
Recommended if some other risk factor is present (e.g., on the basis of medical, occupational, lifestyle, or other indications)

No recommendation

Post Exposure Prophylaxis for Varicella/Zoster

- Determine the risk following exposure:
  - **Pt susceptible?** (bortezomib, no vaccination & no H/O varicella) All immunocompromised pts with H/O varicella can be considered immune, except HSCT recipients.
  - **Exposure significant** enough to result in infection ? (prolonged face-to-face or close indoor contact ≥ 1 h)
  - **Higher risk for complications** (severe immunosuppression)?
- Post-exposure prophylaxis:
  - Acyclovir
  - VariZIG IM within 96 h or 1 dose of IVIG (400 mg/kg)
    - Varicella vaccine 5 mos after VZIG if safe

The Spectrum of Immunosuppression



* Live vaccines

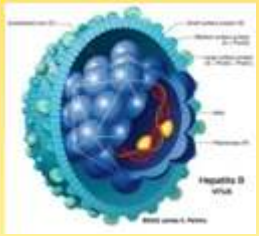
§≥ 1mg/Kg/day prednisone, ≥ 14 days

WHICH VACCINES?

S. pneumoniae

Influenza

Hepatitis B



Determinants of response?

1. ***Streptococcus pneumoniae***
   - Risk factors for invasive disease
     - Defects in humoral immunity
     - Immunosuppressive therapies
     - Renal failure / nephrotic syndrome
     - Asplenia, DM, COPD, CHF
2. **Influenza viruses**
3. **Hepatitis B viruses**
4. **Epidemiologic prevalence**

1. **Remission status**
2. **Immunosuppressive therapies**
   - particularly HD steroids and myeloablative chemotherapy

- Hebrew
- 早安 Chinese
- おはよう Japanese
- ≅Δη Korean
- Καλημέρα Greek
- доброе утро Russian
- Hindi