Side Effects May Include (F031)

American Academy of Dermatology
3/1/2019

Nicole Fett MD MSCE
Associate Professor of Dermatology
Oregon Health and Science University
Conflicts of Interest and Disclosures

- I have no conflicts of interest
- I have no pertinent disclosures
  - UpToDate author and peer reviewer
  - Investigator for Hoffman-La Roche and Pfizer
  - Assistant Section Editor JAMA Derm
  - Education and Program Committee Medical Dermatology Society
  - Education and Program Committee Rheumatologic Dermatology Society
  - Materials review panel medical expert in dermatology for the Lupus Foundation of America
  - Board of Directors Association of Professors of Dermatology
  - President Elect Rheumatologic Dermatology Society
  - AAD Editor, Medical Dermatology Online Board Prep Question Bank
  - Associate Professor of Dermatology, OHSU
  - Dermatology Residency Program Director
  - Packer’s fan and owner
Objectives

• Use the data presented to create a plan for vaccination of your immunosuppressed patients

• Use the data presented to create a plan for prevention of glucocorticoid-induced osteoporosis in your patients on systemic steroids

• Use the data presented to create a plan for pneumocystis pneumonia prevention
Case

Mr. T is a 58 yr old male who presents with a two month history of facial erythema, proximal muscle weakness and new shortness of breath and cough. His PMHx is significant for hepatitis C positivity. He drinks four alcoholic beverages per day. He immigrated to the Pacific Northwest 17 years ago from Vietnam with his wife and two sons.
Case

Which autoantibody is most commonly associated with his disease presentation?

A.) Mi2  
B.) MDA5  
C.) Tif 1γ  
D.) NXP2
Dermatomyositis Antibodies: MDA5

- Cytosolic RNA sensor
- Antibodies to MDA5 in dermatomyositis are linked to:
  - Amyopathic disease
  - Interstitial lung disease
  - Arthritis
  - Cutaneous ulcerations
  - Palmar papules
  - Mechanics hands

Cutaneous findings associated with MDA5 (CADM 140) abs
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Case

Mr. T is found to have interstitial lung disease and myositis and is started on Prednisone 80 mg daily, mycophenolate mofetil 2 gms daily, Hydroxychloroquine 200 mg daily, and nifedipine 60 mg daily. Which of the following vaccines is safe to administer at this time?

A.) Measles, Mumps and Rubella
B.) Nasal influenza
C.) Yellow Fever
D.) Pneumococcal 13-valent conjugate (PCV13)
Case

Mr. T is found to have interstitial lung disease and myositis and is started on Prednisone 80 mg daily, mycophenolate mofetil 2 gms daily, Hydroxychloroquine 200 mg daily, and nifedipine 60 mg daily. Which of the following vaccines is safe to administer at this time?
A.) Measles, Mumps and Rubella
B.) Nasal influenza
C.) Yellow Fever
D.) Pneumococcal 13-valent conjugate (PCV13)
Vaccinations in the Immunosuppressed
EULAR definitions of immunosuppression

• Mildly immunosuppressed
  – < 14 days of corticosteroids
  – < 20 mg/day prednisone or equivalent
  – < 0.4 mg/kg/week methotrexate
  – < 3 mg/kg/day azathioprine
  – < 2.5/mg/kg/day cyclosporine
  – < 0.5 mg/kg/day cyclophosphamide
  – < 0.25 mg/kg/day leflunomide

• Highly immunosuppressed
  – TNF-alpha inhibitors
  – Other biologics
  – Above listed at higher doses

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• Highly immunosuppressed
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Vaccines

• Inactivated Vaccines
  – Influenza injection
  – Tetanus, diptheria, pertussis (Td/Tdap)
  – HPV
  – Pneumococcal polysaccharide (PPSV23)
  – Pneumococcal 13-valent conjugate (PCV13)
  – Meningococcal
  – Hepatitis A
  – Hepatitis B
  – Haemophilus Influenzae b

• Live Attenuated Vaccines
  – Varicella
  – Zoster
  – MMR
  – Nasal influenza
  – Vaccinia
  – Oral polio
  – Oral typhoid
  – *Bacillus Calmette–Guérin*
  – Yellow fever
  – Rotavirus

Always OK, although immunogenecity in immunosuppressed unknown

Risk of reactivation in “immunosuppressed” and therefore should be avoided
Case

Which of the following are recommended by the CDC for all immunocompromised adults?

A.) PPSV23 and PCV13
B.) Meningococcal
C.) Yellow Fever
D.) Hepatitis B
Case

Which of the following are recommended by the CDC for all immunocompromised adults?

A.) PPSV23 and PCV13
B.) Meningococcal
C.) Yellow Fever
D.) Hepatitis B
# CDC Vaccination Recommendations for Immunocompromised Adults

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Pneumonia Vaccine Schedule

**Pneumococcal Vaccine-Naïve Adults**

PCV13 \(\geq 8\) wks → PPSV23 \(\geq 5\) yrs → PPSV23 \(\geq 5\) yrs → PPSV23

**PPSV23-Immunized Adults**

PPSV23 \(\geq 1\) yr → PCV13 \(\geq 8\) wks → PPSV23 \(\geq 5\) yrs → PPSV23

PPSV23 \(\geq 5\) yrs → PPSV23 → PPSV23 \(\geq 5\) yrs

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2018 Combined Recommended Immunization Schedule for Adults Aged 19 Years or Older, United States.  
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2018 Combined Recommended Immunization Schedule for Adults Aged 19 Years or Older, United States. https://www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf
Vaccination Take-Homes

• MMR and Varicella should not be given during immunosuppression
  – Discuss prior infection or vaccination with patients
  – Consider checking titers prior to immunosuppression and giving prior to immunosuppression (4 to 6 weeks)

• All other CDC recommended vaccines for immunocompromised may be given during treatment

• Discuss live vaccines with your patients

• Discuss flu, zoster, pneumo vaccines
Mr. T (who is 58 yo) will likely be on prednisone for at least 6 months given his myositis and interstitial lung disease. As a reminder, he was started on 80 mg daily of prednisone (1 mg/kg/day). Which of the following is true in regards to prevention of glucocorticoid-induced osteoporosis?

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C.) Mr. T should be prescribed calcium, vitamin D and a bisphosphonate now
D.) Mr. T should be prescribed calcium, vitamin D and teriparatide now
Glucocorticoids and Bone

30–50% of chronic glucocorticoid users develop a fracture
Corticosteroid-induced Bone Loss

- Rapid decline in BMD during first 3 mos of glucocorticoid therapy
  - Peak at 6 mos
  - Gradual loss thereafter
  - Doses > 2.5 mg per day increase risk of vertebral and non-vertebral fracture


http://courses.washington.edu/bonephys/tx/
Corticosteroids and Bone

• Highest rate of bone loss occurs in the first 6 mos

• Low doses of corticosteroids increase fracture risk

• Short course of corticosteroids increase fracture risk
Hip Fractures Increase Risk of Mortality

2017 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis

LENORE BUCKLEY,¹ GORDON GUYATT,² HOWARD A. FINK,³ MICHAEL CANNON,⁴ JENNIFER GROSSMAN,⁵ KAREN E. HANSEN,⁶ MARY BETH HUMPHREY,⁷ NANCY E. LANE,⁸ MARINA MAGREY,⁹ MARC MILLER,¹⁰ LAKE MORRISON,¹¹ MADHUMATHI RAO,¹² ANGELA BYUN ROBINSON,¹³ SUMONA SAHA,⁶ SUSAN WOLVER,¹⁴ RAVEENDHARA R. BANNURU,¹² ELIZAVETA VAYSBROT,¹² MIKALA OSANI,¹² MARAT TURGUNBAEV,¹⁵ AMY S. MILLER,¹⁵ AND TIMOTHY MCALENDON¹²
ACR scope

• For everyone taking GC >2.5 mg/day for > 3 mos
• Inhaled Glucocorticoids not included
• Renal failure (GF < 30 ml/min) not included
• Two groups, ≥ 40, < 40
  – Not enough data for prediction tools < 40 yrs
• GRADE methodology
  – Recommendations based on relative benefits and harms, quality of evidence, and patient values and preferences

Risk Stratifying Our Patients


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**Calculation Tool**

Please answer the questions below to calculate the ten year probability of fracture with BMD.

**Questionnaire:**

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
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<td>2. Sex</td>
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</tr>
<tr>
<td>3. Weight (kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Height (cm)</td>
<td></td>
<td></td>
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<tr>
<td>5. Previous Fracture</td>
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<td>7. Current Smoking</td>
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**Weight Conversion**

Pounds ➔ kg

**Height Conversion**

Inches ➔ cm

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05914760

Individuals with fracture risk:
## Fracture Risk Assessment

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<td></td>
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<tr>
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Hip or spine BMD T score ≤ -2.5 in men ≥ 50 and PMW  
FRAX (*1.15 non-hip fracture if taking > 7.5 mg/day) 10 yr risk non-hip fracture ≥ 20%  
FRAX (*1.2 hip fracture if taking > 7.5 mg/day) 10 yr risk hip fracture ≥ 3% | Prior osteoporotic fracture |
| **Moderate Fracture Risk** | FRAX (*1.15 non-hip fracture if taking > 7.5 mg/day) 10 yr risk non-hip fracture 10-19%  
FRAX (*1.2 hip fracture if taking > 7.5 mg/day) 10 yr risk hip fracture >1 and <3% | Hip or spine BMD Z score < -3 OR Rapid bone loss (≥10% at hip or spine over 1 year)  
AND  
Continuing GC at > 7.5 mg/day for ≥ 6 mos |
| **Low Fracture Risk** | FRAX (*1.15 non-hip fracture if taking > 7.5 mg/day) 10 yr risk non-hip fracture <10%  
FRAX (*1.2 hip fracture if taking > 7.5 mg/day) 10 yr risk hip fracture ≤1% | None of the above risk factors other than GC treatment |

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Counseling for EVERYONE on Glucocorticoids

- Calcium intake of 1200 to 1500 mg/day
- Vitamin D supplementation
- Weight bearing activities
- Smoking cessation
- Avoid > 2 ETOH/day
- Maintain normal body weight

Figure 3. Initial pharmacologic treatment for adults.

- Calcium and Vitamin D and Lifestyle Modifications
  
  - Low Risk
    
    No Further Treatment
    Monitor with yearly clinical fracture risk assessment with BMD testing every 2-3 years depending on risk factors.
Figure 3. Initial pharmacologic treatment for adults.

- **Calcium and Vitamin D and Lifestyle Modifications**
- **Moderate/High Risk**
  - Children ages 4–17 years with an osteoporotic fracture who are continuing treatment with GCs at a dose of ≥0.1 mg/kg/day for ≥3 months
    - Treat with an oral bisphosphonate (IV bisphosphonate if oral treatment contraindicated) plus calcium and vitamin D over treatment with calcium and vitamin D alone.
    - **Conditional recommendation** because of very low-quality antifracture data in children but moderate-quality evidence of low harms of oral bisphosphonates in children and less potential harm of oral over IV bisphosphonates.
  - 4. FRAX (GC-adjusted) 10-year risk for hip fracture > 1% OR
  - 5. Very high dose GCs

- **Women of Childbearing Potential** (not planning a pregnancy during period of OP treatment)
  - Treat with an oral bisphosphonate
    - Second-line therapy: teriparatide
    - Other suggested therapies (in order of preference) for high-risk women for whom the previous drugs are not appropriate:
      - IV bisphosphonates
      - denosumab
- **Women Not of Childbearing Potential and Men**
  - Treat with an oral bisphosphonate
    - Other suggested therapies (in order of preference):
      - IV bisphosphonates
      - teriparatide
      - denosumab
      - raloxifene for PMP women if no other therapy is available
Who needs a bisphosphonate on day 1?

- Any age with h/o OP fracture
- Age ≥ 30 yrs and very high dose GC*
- Age < 40 yrs
  - Z score < -3 and prednisone ≥ 7.5mg/day*
  - > 10% BMD loss/yr on prednisone ≥ 7.5mg/day*
- Men ≥ 50 yrs and Post-menopausal women
  - T score ≤ 2.5
  - OP FRAX ≥ 10%
  - Hip FRAX > 1%

*Not planning a pregnancy during treatment
Mr. T (who is 58 yo) will likely be on prednisone for at least 6 months given his myositis and interstitial lung disease. As a reminder, he was started on 80 mg daily of prednisone (1 mg/kg/day). Which of the following is true in regards to prevention of glucocorticoid-induced osteoporosis?

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Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Questionnaire:

1. Age (between 40 and 90 years) or Date of Birth
   Age: 58
   Date of Birth: [ ] M: [ ] D: [ ]

2. Sex
   [ ] Male  [ ] Female

3. Weight (kg)
   78

4. Height (cm)
   165

5. Previous Fracture
   [ ] No  [ ] Yes

6. Parent Fractured Hip
   [ ] No  [ ] Yes

7. Current Smoking
   [ ] No  [ ] Yes

8. Glucocorticoids
   [ ] No  [ ] Yes

9. Rheumatoid arthritis
   [ ] No  [ ] Yes

10. Secondary osteoporosis
    [ ] No  [ ] Yes

11. Alcohol 3 or more units/day
    [ ] No  [ ] Yes

12. Femoral neck BMD (g/cm²)

Select BMD

[ ] No  [ ] Yes

BMI: 28.7
The ten year probability of fracture (%)
without BMD

Major osteoporotic: 8.0%
Hip Fracture: 0.8%

X 1.15 = 9.2

X 1.2 = 0.96

Calcium and Vitamin D and Lifestyle Modifications

Moderate/High Risk

Age < 40 Years
1. History of OP fracture(s) OR
2. Z score ≤ −3 at hip or spine and prednisone ≥ 7.5 mg per day OR
3. > 10% per year loss of BMD at hip or spine and prednisone ≥ 7.5 mg per day OR
4. Very high dose GCs and ≥ 30 years

Age ≥ 40 Years
1. History OP fracture(s) OR
2. Men ≥ 50 years and PMP women with a BMD T score ≤ −2.5 at the hip or spine OR
3. FRAX (GC-adjusted) 10-year risk for major osteoporotic fracture ≥ 10% OR
4. FRAX (GC-adjusted) 10-year risk for hip fracture > 1% OR
5. Very high dose GCs

Women Not of Childbearing Potential and Men

Treat with an oral bisphosphonate
Other suggested therapies (in order of preference):
IV bisphosphonates
teriparatide
denosumab
r aloxifene for PMP women if no other therapy is available.
Mr. T’s returns for follow up 2 weeks later. His labs result and reveal an albumin of 2 and lymphocytes of 800. He remains on prednisone 80 mg, mycophenolate mofetil 2 gms per day, hydroxychloroquine 200 mg daily and nifedipine 60 mg daily. He has also started calcium 1200 mg daily, vitamin D 1000 units daily and alendronate 70 mg weekly. At this point would you start PCP prophylaxis?

A.) Yes
B.) No
Why is PCP prophylaxis in medical dermatology patients difficult?

- The risk of developing PCP is very very small
  - Risk factors not well defined
  - Extrapolated from other patient populations
- The mortality associated with non-HIV PCP is very high
- Prophylaxis is very effective
- There are costs, side effects and potential mortality associated with prophylaxis
<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Setting</th>
<th>Diagnoses</th>
<th>#Patients</th>
<th>#PCP</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lehman et al.</td>
<td>2010</td>
<td>One tertiary medical center in MN</td>
<td>Psoriasis, SLE, DM, Pemphigoid, many others</td>
<td>198</td>
<td>1</td>
<td>0.5%</td>
</tr>
<tr>
<td>Gerhart et al.</td>
<td>2010</td>
<td>One tertiary medical center in MN.</td>
<td>CTD and ABD</td>
<td>334</td>
<td>7</td>
<td>2.1%</td>
</tr>
<tr>
<td>Li et al.</td>
<td>2011</td>
<td>One tertiary medical center in China</td>
<td>ABD</td>
<td>202</td>
<td>4</td>
<td>1.9%</td>
</tr>
<tr>
<td>Leshem et al.</td>
<td>2014</td>
<td>One tertiary medical center in Israel</td>
<td>Pemphigus</td>
<td>172</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Amber et al.</td>
<td>2017</td>
<td>6 tertiary medical centers (Germany, Italy, Israel, Singapore, Netherlands)</td>
<td>ABD</td>
<td>801</td>
<td>1</td>
<td>0.1%</td>
</tr>
<tr>
<td>Rekhtman et al.</td>
<td>2018</td>
<td>Multi-health system</td>
<td>On IS, GC, or IS+GC vs none</td>
<td>29,020,380</td>
<td>1340</td>
<td>0.0138% – 0.2775%</td>
</tr>
</tbody>
</table>
Harms of TMP-Sulfa


<table>
<thead>
<tr>
<th>Study Patient population</th>
<th>TMP-SMX</th>
<th>Control</th>
<th>Other therapy</th>
<th>Risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-HIV immunocompromised patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any adverse</td>
<td>70/245</td>
<td>65/225</td>
<td>--</td>
<td>1.01 (0.82–1.24)</td>
</tr>
</tbody>
</table>

NNH ~32 serious adverse events
NNT vs NNH

TABLE 2. NNT to Prevent 1 PCP Infection With TMP-SMX Prophylaxis for Ascending Attack Rates of PCP*

<table>
<thead>
<tr>
<th>Control event rate†</th>
<th>NNT</th>
<th>Clinical conditions associated with specific attack rates among immunocompromised non–HIV-infected patients⁹</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>11</td>
<td>Allogeneic bone marrow transplant, acute lymphoblastic leukemia, solid organ transplant, severe combined immunodeficiency syndrome</td>
</tr>
<tr>
<td>0.035†</td>
<td>32†</td>
<td>Wegener granulomatosis, rhabdomyosarcoma</td>
</tr>
<tr>
<td>0.015</td>
<td>73</td>
<td>Hodgkin disease, central nervous system tumors, polymyositis/dermatomyositis</td>
</tr>
<tr>
<td>0.01</td>
<td>110</td>
<td>Systemic lupus erythematosus, polyarteritis nodosa, scleroderma, pemphigus, pemphigoid, other long-term corticosteroid treatment</td>
</tr>
<tr>
<td>0.001</td>
<td>1099</td>
<td>Rheumatoid arthritis</td>
</tr>
</tbody>
</table>

What if we could predict those patients who were most at risk of PCP and only provide prophylaxis to those patients?
Risk Factors for the Development of PCP

Li et al. Independent predictors of PcP.*

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3+ cell count &lt; 625 x 10^6/l</td>
<td>12.5</td>
<td>(2.4–65.1)</td>
<td>0.003</td>
</tr>
<tr>
<td>Serum albumin &lt; 28 g/l</td>
<td>7.3</td>
<td>(1.7–32.4)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Messiaen P et al. The role of CD4-cell count as discriminatory measure to guide chemoprophylaxis against Pneumocystis jiroveci pneumonia in human immunodeficiency virus-negative immunocompromised patients: A systematic review. Transpl Infect Dis. 2017. 19:e12651/
Risk Factors for the Development of PCP


Messiaen P et al. The role of CD4-cell count as discriminatory measure to guide chemoprophylaxis against Pneumocystis jirovecii pneumonia in human immunodeficiency virus-negative immunocompromised patients: A systematic review. Transpl Infect Dis. 2017. 19:e12651
Risk Factors for the Development of PCP

- Low lymphocytes (<1000)
- Low CD3 (<625)
- Low CD4 (<200)
- Low CD8 (<150)
- Low albumin (2.8)
- Lung disease (ILD, CMV)
- High doses of prednisone
- Multiple immunosuppressants
Risk Factors for the Development of PCP

- Low lymphocytes (<1000)
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PCP Take Homes

• The risk of developing PCP for medical dermatology patients is very very small

• PCP-associated mortality is very high

• Patients on high doses of prednisone (30 mg daily), with low albumin, low lymphocytes, low CD3, CD4, CD8 cells, and those with ILD may benefit the most from prophylaxis