Pneumocystis jiroveci Pneumonia:
Prophylaxis in Immunocompromised States

September 20th, 2019

Arsany Gadallah, PharmD, MBA
PGY-1 Pharmacy Corporate Resident
Ascension Seton
Arsany.Gadallah@ascension.org
Table of Contents

Presentation Slides.................................................................Pages 3 to 10
Appendix A: Abbreviations.........................................................Page 11
Appendix B: Fillatre, et al. Figure................................................Page 12
Appendix C: Schmajuk, et al. Figures..........................................Page 13
Learning Objectives

• Describe the epidemiology and pathophysiology of *Pneumocystis jirovecii* Pneumonia (PJP)
• Review the clinical presentation and prophylaxis for the disease
• Identify risk factors and susceptible patients for PJP
• Explore clinical studies comparing the efficacy and safety of PJP prophylaxis in HIV-negative and non-chemotherapy patients

Patient Case

• GA is a 34 year-old female who presents to the emergency department with right ear pain/abscess. A moderate amount of fluid was drained surgically and the patient was discharged on ciprofloxacin 500 mg twice daily for 7 days with next-day ENT referral.
• After 3 days, GA starts to experience pain in her jaw (bilateral), right elbow, right neck, hips, knees and 2-3 hours of morning stiffness in left hand. Imaging showed nodules on left ear and nasal septum.
• GA was admitted to the hospital for suspected relapsing polyarthritis, for which she was started on methylprednisolone 1 gram IV daily and oral methotrexate 15 mg weekly

Should *Pneumocystis jiroveci* Pneumonia (PJP) prophylaxis be initiated?

a) YES
b) NO

*Pneumocystis (carinii) jiroveci* Pneumonia (PJP)

• Carlos Chagas first to discover cystic forms of Pneumocystis in 1909
• In 1910, *Antonio Carini* found similar cystic forms in the lungs of rats - named *Pneumocystis carinii*
• In the 1940s, *Pneumocystis* was linked to pneumonia in premature and malnourished infants
• In 1952, *Otto Jirovec* identified this organism as the causative agent of interstitial pneumonia in infected infants
• In 1980s, PJP became more prevalent with the widespread of human immunodeficiency virus (HIV)
**Background**

- Pneumocystis organisms are fungi that were initially classified as a protozoa due to different forms
- Lack of ergosterol and difficult to be cultured
- Three distinct morphological stages: trophic form (clusters), precystic form (sporozoite) and cyst form (spores)
- Pneumocystis organisms are commonly found in healthy lungs with earliest exposures reported by age 4 years
- Pneumocystis organisms are communicable via airborne transmission
- Pneumonia occurs when both cellular and humoral immunity are defective

**Epidemiology**

- PJP was the most common opportunistic infection in the years 2008-2010
- CDC reports near 40% of PJP patients are HIV positive and 60% are immunocompromised due to other states
- Mortality rates reported in Non-HIV (nHIV) patients range between 30-50%, compared to 10-12% in HIV patients
- Up to 20% of adults could be carriers at any given point without any symptoms
- Eradication by healthy immune system could take several months

**Pathophysiology**

- The trophic form of *Pneumocystis jiroveci* attaches to the alveoli and replicates freely under immune suppression
- Macrophages are unable to eradicate these organisms without CD4+ cells
- Inflammatory response leads to symptoms of:
  - Hypoxemia
  - Respiratory alkalosis
  - Impaired diffusing capacity
  - Changes in vital capacity
  - Respiratory failure

**Clinical Presentation**

- PJP in HIV patients presents gradually and progresses to respiratory failure in 2 weeks - 2 months
- Easier to diagnose in HIV patients due to larger fungal load in lungs
- PJP in nHIV* (immunocompromised) patients has an abrupt onset and progresses to respiratory failure in 1 week
- Respiratory insufficiency is more severe in nHIV patients
- More severe inflammatory response in nHIV patients (more bronchoalveolar neutrophils)
- Other symptoms include:
  - Fever and non-productive cough (HIV = nHIV)
  - Chest pain (HIV > nHIV)
  - Weight loss (HIV > nHIV)

*Includes transplant and chemotherapy patients

**Diagnosis: Laboratory Indices**

<table>
<thead>
<tr>
<th>Diagnostic Index</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum Sample</td>
<td>Variable (55-59%)</td>
<td>High (99-100%)</td>
</tr>
<tr>
<td>Bronchoalveolar Lavage (BAL)</td>
<td>High (&gt;95%)</td>
<td>High (99-100%)</td>
</tr>
<tr>
<td>Polymerase Chain Reaction (PCR)</td>
<td>High (94-100%)</td>
<td>High (79-96%)</td>
</tr>
<tr>
<td>Lactic Dehydrogenase (LDH)</td>
<td>Variable</td>
<td>Low</td>
</tr>
<tr>
<td>Pulmonary Function Tests</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>L-3,β-D-glucan Blood test (BDG)</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Lung Tissue Biopsy</td>
<td>Highest</td>
<td>Highest</td>
</tr>
</tbody>
</table>

**Diagnosis: Imaging**

- Chest radiography (CXR)
  - Diffuse bilateral infiltrates
- Chest high-resolution computed tomography scan (CT)
  - Bilateral ground-glass opacities
### Treatment

- **First-line:** Trimethoprim-sulfamethoxazole
- **Second-line:** Atovaquone/Pentamidine/Dapsone
- **Salvage:** Clindamycin
- **Adjunctive:** Corticosteroids (for PaO2 <70)
  - Prednisone/prednisolone

### Prophylaxis

- **First-line:** Trimethoprim-sulfamethoxazole (TMP-SMX)
  - Double-strength (DS: 160 mg TMP-800 mg SMX) 1 tablet by mouth (PO) daily
  - Single Strength (SS: 80 mg TMP-400 mg SMX) 1 tablet PO daily
- **Second-line:**
  - **TMP-SMX** 1 DS tablet PO three times weekly
  - **Dapsone** 100 mg PO daily or 50 mg PO twice daily
    - Clindamycin 30 mg PO daily + pyrimethamine 50 mg PO weekly + leucovorin 25 mg PO weekly
  - **Atovaquone** 1500 mg PO daily + pyrimethamine 25 mg PO daily with leucovorin 10 mg PO daily
  - **Pentamidine** 300 mg in 6 mL sterile water nebulized every 4 weeks

### Populations At Risk

- According to the National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), and the HIV Medicine Association of the Infectious Diseases Society of America (IDSA):
  - HIV-infected patients with:
    - CD4+ count below 200 cells/microl (A1)
    - Oral thrush (A1)
    - CD4+ less than 14% of total lymphocyte count (BII)
    - CD4+ of 200-250 cells/microl when antiretroviral treatment (ART) cannot be started (BIII)
    - Inability to monitor CD4+ count every 3 months (BIII)

### Other Populations?

- **Connective Tissue Disorders**
  - Granulomatosis with polyangiitis (GPA)
  - Reported risk between 0.88% to 6%
  - Dermatomyositis/polymyositis (PM/DM)
  - Reported increasing risk
  - Disorders requiring immunosuppressive/corticosteroid therapy
  - Reported increasing risk due to emergence of biologics
- **Rheumatoid arthritis (RA)**
  - Reported low risk (0.02%)
- **Inflammatory Bowl Diseases (IBD)**
  - Few reports/low rates due to younger patients

### Risk Factors

- Immunocompromised
- HIV
- nHIV
- Colonization
- Cancer
- Solid organ transplant
- Hematopoietic stem cell transplant

### Populations At Risk Cont’d

- According to the European Conference on Infections in Leukemia (ECIL):
  - Patients receiving glucocorticoid doses greater than 20 mg daily for at least one month (Expert)
  - Bone marrow suppression therapies or antineoplastic therapies (Expert)
  - Patients undergoing hematopoietic cell/solid organ transplant (BIII)

### Other Populations?

- **Connective Tissue Disorders**
  - Granulomatosis with polyangiitis (GPA)
  - Reported risk between 0.88% to 6%
  - Dermatomyositis/polymyositis (PM/DM)
  - Reported increasing risk
  - Disorders requiring immunosuppressive/corticosteroid therapy
  - Reported increasing risk due to emergence of biologics
- **Rheumatoid arthritis (RA)**
  - Reported low risk (0.02%)
- **Inflammatory Bowl Diseases (IBD)**
  - Few reports/low rates due to younger patients
Risk-Benefit Analysis

The Risks

<table>
<thead>
<tr>
<th>Notable Side Effects/Cautions</th>
<th>Ext. Cost-per-month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethoprim-sulfamethoxazole (oral)</td>
<td>GI discomfort, hypersensitivity reactions, elevated creatinine, hyperkalemia, Stevens-Johnson Syndrome (50$)</td>
</tr>
<tr>
<td>Dapsone (oral)</td>
<td>G6PD testing, Anemia, hemolyis, methemoglobinemia</td>
</tr>
<tr>
<td>Atovaquone (oral)</td>
<td>Nausea, diarrhea, rash, hepatitis</td>
</tr>
<tr>
<td>Pentamidine (aerosolized)</td>
<td>Cough, bronchospasm, wheezing, pneumothorax, fever, pancreatitis</td>
</tr>
</tbody>
</table>

Fillatre et al.

Potential Benefit Groups

- A retrospective analysis by Fillatre et al. estimates incidence rates within each disease state documented at their institution
- Study population
  - 293 cases of PJP documented from 1990 to 2010
  - Positive bronchoalveolar lavage + PCR
  - Excluded HIV-positive patients

Fillatre et al.

Fillatre et al.

Incidence rate

% of total PJP cases (nHIV)

- Vasculitis 9%
- Inflammatory Diseases 14%
- Infectious Diseases 1%
- Rheumatoid Arthritis (0.5%)
- Polyarteritis Nodosa (0.2%)
- Other (7%)
- Solid Organ Transplant (11%)
- Solid Tumors (18%)
- Others (9%)

Fillatre et al.

Incidence rate

Vasculitis

- Polyarteritis nodosa (1.9%)
- Granulomatosis with Polyangiitis (1.5%)
- Giant cell arteritis (0.2%)

Fillatre et al.

Incidence rate

Vasculitis

- Granulomatosis with Polyangiitis (1.5%)
- Polyarteritis Nodosa (0.2%)
- Rheumatoid Arthritis (0.5%)
- Other (7%)

Fillatre et al.

Incidence rate

Inflammatory Diseases

- Rheumatoid Arthritis (0.5%)
- Polyarteritis Nodosa (0.2%)
- Other (7%)

Fillatre et al.

Incidence rate

Inflammatory Diseases

- Polyarteritis Nodosa (0.2%)
- Rheumatoid Arthritis (0.5%)
- Other (7%)

Fillatre et al.

Incidence rate

Hematological Malignancies

- 30%

Fillatre et al.

Incidence rate

Solid Tumors

- 25%

Fillatre et al.

Incidence rate

Others

- 11%

Fillatre et al.

Incidence rate

Glomerulonephritis*
- 1%

Fillatre et al.

Incidence rate

Interstitial Lung Disease*
- 2%

Fillatre et al.

Incidence rate

Cirrhosis*
- 3%
The Benefits: Rheumatic Diseases

- A retrospective study by Schmajuk et al. explored practice patterns of PJP prophylaxis in rheumatic diseases at the University of California – San Francisco
- Study population composed of 316 patients followed for an average of 23.1 months:
  - A diagnosis of granulomatosis with polyangiitis (GPA), Microscopic Polyangiitis (MPA), dermatomyositis (DM), polymyositis (PM), or Systemic Lupus Erythematosus (SLE)
  - At least 1 of the following immunosuppressants: azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil, rituximab, and prednisone 10 mg daily or equivalent
  - Excluded: age below 18 years, any diagnosis of HIV/AIDS, pregnancy, active malignancy, and solid organ transplant.

### Schmajuk et al.

- **Primary Endpoint**
  - Prescription for PJP prophylaxis after initiating immunosuppression
- **Results**
  - Out of the 316 patients, 124 (39%) of patients received qualifying prophylactic antibiotics
  - TMP-SMX (73%), dapsone (16%), atovaquone (10%), pentamidine (1%)

<table>
<thead>
<tr>
<th>Immunosuppressant</th>
<th>% of Patients Receiving PJP Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>77%</td>
</tr>
<tr>
<td>Rituximab</td>
<td>68%</td>
</tr>
<tr>
<td>Glucocorticoid</td>
<td>30%</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>33%</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>21%</td>
</tr>
</tbody>
</table>

- **Authors’ interpretation:**
  - Incidence rate of PJP in the non-prophylaxis group was 3.7/375 patient-years (1% per year)
  - Findings show efficacy of selective use of PJP prophylaxis in high-risk diagnoses and immunosuppressants
  - Due to significant rate of adverse events (2.2% per year), PJP prophylaxis should be personalized
- **Limitations:**
  - Excluding antibiotic prescription ordered for less than 30 days (29 patients)
  - Single center without a standard diagnostic process

### The Benefits: Rheumatoid Arthritis (RA)

- A retrospective cohort study conducted by Yukawa et al. shows increasing incidence of PJP in rheumatoid arthritis patients based on certain risks
  - 2,640 RA patients from 2010 to 2014, 19 patients developed PJP
  - Diagnosis was based on respiratory samples (microscopic examination OR positive PCR + positive 1,3-β-D-glucan (BDG))
  - PJP patients were hospitalized over an average period of 5 days
  - TMP/SMX was changed to pentamidine in 3 patients due to adverse events
  - Thrombocytopenia, skin eruptions, hypotension, vomiting
  - 15 patients tolerated treatment, 4 patients died due to pulmonary failure secondary to bacterial/viral infections
**Yukawa et al.**

- **Primary outcome:** Incidence rate of PJP in rheumatoid arthritis based on risk factors present
- **Results:**
  - Scoring system based on odds ratios (OR)
    - Methotrexate ≥ 6 mg/wk, OR = 4.5 (1 point)
    - Age ≥ 65 years, OR = 3.7 (1 point)
    - ≥ 2 immunosuppressants, OR = 3.7 (1 point)
    - Methotrexate, azathioprine, leflunomide, cyclosporine, tacrolimus
    - Infliximab, etanercept, golimumab, certolizumab, tocilizumab, abatacept
    - Prednisolone ≥ 5 mg/day, OR = 12.4 (3 points)

**Conclusion:**

CAP prophylaxis may not be necessary in RA patients unless risk score is at least 5 points.

**Limitations**

- Single center study
- Using odds ratios may not depict true severity of risk factors
- Diagnosis was not standardized

---

**Metraiah et al.**

- **Primary outcome**
  - Onset of PJP from the time of diagnosis of AAV in patients
- **Results**
  - Majority (75%) of AAV patients were positive for GPA
  - 14 out of the 16 PJP+ patients had received co-trimoxazole prophylaxis during induction phase (first 3-6 months) – not reintroduced during escalation of immunosuppression
  - 2 patients were intolerant to treatment and proceeded with clindamycin + primaquine combination
  - 2 patients died accounting for mortality rate of 12.5% in PJP+ group
  - The median time from AAV diagnosis to PJP was 8 months
  - Lymphopenia was present in all AAV cases

**Authors’ Interpretation**

- PJP could occur after the induction phase in AAV, especially during escalation of immunosuppressants
- Extended PJP prophylaxis might be valuable when augmented immunosuppression is given, especially in patients with lymphopenia (potential risk factor)

**Limitations**

- Single center study
- 2 PJP patients missing information
- Different immunosuppression regimen during maintenance

---

**The Benefits: Vasculitis**

- A retrospective cohort by Metraiah et al. analyzes all institutional PJP positive cases with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) to determine onset of PJP infection
- **Study population**
  - 142 patients with positive PJP PCR from April of 2006 to July of 2016
  - 16 PJP+ and AAV+ patients were identified and studied retrospectively
  - Immunosuppressants used with steroid therapy during induction and maintenance phases:
    - Cyclophosphamide (first-line for induction), rituximab, mycophenolate mofetil, azathioprine (first-line for maintenance), methotrexate

**Primary outcome:**

- Onset of PJP from the time of diagnosis of AAV in patients

**Results**

- Majority (75%) of AAV patients were positive for GPA
- 14 out of the 16 PJP+ patients had received co-trimoxazole prophylaxis during induction phase (first 3-6 months) – not reintroduced during escalation of immunosuppression
- 2 patients were intolerant to treatment and proceeded with clindamycin + primaquine combination
- 2 patients died accounting for mortality rate of 12.5% in PJP+ group
- The median time from AAV diagnosis to PJP was 8 months
- Lymphopenia was present in all AAV cases

**Authors’ Interpretation**

- PJP could occur after the induction phase in AAV, especially during escalation of immunosuppressants
- Extended PJP prophylaxis might be valuable when augmented immunosuppression is given, especially in patients with lymphopenia (potential risk factor)

**Limitations**

- Single center study
- 2 PJP patients missing information
- Different immunosuppression regimen during maintenance

---

**The Benefits: Inflammatory Bowel Disease (IBD)**

- A retrospective cohort study by Long et al. compares in the incidence of PJP in IBD patients compared to non-IBD patients.
- **Study population**
  - IBD patients of 64 years of age and younger
  - 50,932 patients with Crohn’s Disease (CD); 56,403 with Ulcerative Colitis (UC); 1,269 with unspecified IBD; compared to 434,416 with non-IBD
  - All patients were required to have at least 12 months of continuous health plan and pharmacy coverage (to capture medication history)
  - At least 1 pharmacy claim for:
    - Mesalamine, olsalazine, balsalazide, sulfasalazine, 6-mercaptopurine, azathiopurine, methotrexate, infliximab, adalimumab, certolizumab, natalizumab, and enteral budesonide
  - All individuals with any ICD-9 code for HIV were excluded

---

**The Benefits: Vasculitis**

- A retrospective cohort by Metraiah et al. analyzes all institutional PJP positive cases with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) to determine onset of PJP infection
- **Study population**
  - 142 patients with positive PJP PCR from April of 2006 to July of 2016
  - 16 PJP+ and AAV+ patients were identified and studied retrospectively
  - Immunosuppressants used with steroid therapy during induction and maintenance phases:
    - Cyclophosphamide (first-line for induction), rituximab, mycophenolate mofetil, azathioprine (first-line for maintenance), methotrexate

**Primary outcome:**

- Incidence rate of PJP in rheumatoid arthritis based on risk factors present

**Results:**

- Scoring system based on odds ratios (OR)
  - Methotrexate ≥ 6 mg/wk, OR = 4.5 (1 point)
  - Age ≥ 65 years, OR = 3.7 (1 point)
  - ≥ 2 immunosuppressants, OR = 3.7 (1 point)
  - Methotrexate, azathioprine, leflunomide, cyclosporine, tacrolimus
  - Infliximab, etanercept, golimumab, certolizumab, tocilizumab, abatacept
  - Prednisolone ≥ 5 mg/day, OR = 12.4 (3 points)

**Conclusion:**

- CAP prophylaxis may not be necessary in RA patients unless risk score is at least 5 points

**Limitations**

- Single center study
- Using odds ratios may not depict true severity of risk factors
- Diagnosis was not standardized
Summary of Literature

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk Population (nHIV)</th>
<th>PJP Prophylaxis Recommended?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fillatre et al.</td>
<td>Inflammatory diseases, vasculitis</td>
<td>Only in vasculitis (GPA, PAN) &amp; PM/DM</td>
</tr>
<tr>
<td>Schmajuk et al.</td>
<td>GPA, PM, DM, SLE</td>
<td>No</td>
</tr>
<tr>
<td>Yukawa et al.</td>
<td>RA</td>
<td>Only for scores 5 and above</td>
</tr>
<tr>
<td>Medraiah et al.</td>
<td>AAV</td>
<td>Yes (reduction and maintenance)</td>
</tr>
<tr>
<td>Long et al.</td>
<td>IBD</td>
<td>Depends on other factors</td>
</tr>
</tbody>
</table>

Back to GA

• Do you recommend starting PJP prophylaxis?
  • YES
  • NO

GA is a 34-year-old female admitted for relapsing polychondritis with lymphocytopenia

GA has a complex autoimmune disorder (PR3+)

GA is on cyclophosphamide, prednisone and methotrexate

Multiple readmissions for abscess and ear pain

Conclusion

• Immunosuppression is key in developing PJP
• Initiating PJP prophylaxis should be based on all risk factors present in the patient
• More studies are needed to evaluate the severity of each risk factor
• In some disease states, such as rheumatoid arthritis and systemic lupus erythematosus, risks may outweigh the benefit of PJP prevention
• In high-risk disease states, such as vasculitis, prophylaxis may be necessary

Future Direction

• Lack of randomized controlled trials is impeding implementation of new recommendations into practice guidelines
• Comparing safety and efficacy of different prophylaxis regimens in the HHIV population
• PJP risk does not take into account other important factors, such as patient-level differences in drug metabolism
• Pharmacy involvement to help individualize PJP prophylaxis based on patient-specific attributes
References


Appendix A

Abbreviations

- AAV- Anti-neutrophil cytoplasmic antibody Associated Vasculitis
- ART- Antiretroviral Treatment
- BAL- Bronchoalveolar Lavage
- BDG- 1,3-β-D-Glucan blood test
- BP- Blood Pressure
- CD- Crohn’s Disease
- CDC- Centers for Disease Control and Prevention
- CI- Confidence Interval
- CRP- C-reactive Protein
- CT- Computed Tomography
- CXR- Chest X-ray
- DM- Dermatomyositis
- DS- Double Strength
- eCrCl- Estimated Creatinine Clearance
- ENT- Ears, Nose, and Throat
- ESR- Erythrocyte Sedimentation Rate
- G6PD- Glucose-6-Phosphate Dehydrogenase
- GPA- Granulomatosis with Polyangiitis
- HIV- Human Immunodeficiency Virus
- HR- Heart Rate
- Ht- Height
- IBD- Inflammatory Bowl Diseases
- ICD- International Classification of Diseases
- IRR- Incidence Rate Ratio
- IV- Intravenous
- LDH- Lactic Dehydrogenase
- nHIV- Non- HIV population
- NNT- Number Needed to Treat
- PAN- Polyarteritis Nodosa
- PCR- Polymerase Chain Reaction
- PJP- *Pneumocystis jiroveci* Pneumonia
- PM- Polymyositis
- PMH- Past Medical History
- PO- Oral
- PR3- Proteinase
- RA- Rheumatoid Arthritis
- RR- Respiratory Rate
- SLE- Systemic Lupus Erythematosus
- SS- Single Strength
- TMP-SMX- Trimethoprim-sulfamethoxazole
- UC- Ulcerative Colitis
- WBC- White Blood Cell
- Wt- Weight
Appendix B

Figure 1. Fillatre et al.: Incidence of PJP across study disease states
Appendix C

Figure 2. Schmajuk et al.: Rate of patients receiving PJP prophylaxis in each disease state

Figure 3. Schmajuk et al.: Rate of adverse events associated with PJP Prophylaxis