Steroids Aren't Always Innocent

Evaluating the Risk of *Pneumocystis jirovecii* Pneumonia with Prolonged Corticosteroid Use

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Disclosures

The planner(s) and speaker(s) have indicated that there are no relevant financial relationships with any ineligible companies to disclose.

Abbreviations Key

- AIRDS = Autoimmune inflammatory rheumatic disease
- ANCA = Anti-Neutrophil Cytoplasmic Antibody
- ATG = Anti-thymocyte globulin
- BAL = Bronchioalveolar lavage
- BDG = 1,3-Beta-D Glucan Test
- COX = Cyclooxygenase
- CrCl = Creatinine clearance
- DNA = Deoxyribonucleic acid
- EULAR = European Alliance of Association for Rheumatology
- FN= False negative
- FP= False positive
- GVHD = Graft-versus host disease
- HIV = Human Immunodeficiency Virus
- HSCT = Hematopoietic stem cell transplant
- ICU = Intensive care unit
- IL = Interleukin
- INF = Interferon
- MMF = Mycophenolate mofetil
- N/V = Nausea/vomiting
- NF-κB = Nuclear factor kappa beta
- PCR = Polymerase chain reaction
- PJP = Pneumocystis jirovecii pneumonia
- RNA = Ribonucleic acid
- RT-PCR= Reverse Transcriptase polymerase chain reaction
- SJS = Steven Johnson syndrome
- SOT = Solid organ transplant
- TNF = Tumor necrosis factor
- TMP-SMX = Trimethoprim and sulfamethoxazole
- VEGF = Vascular endothelial growth factor

Learning Objectives

1. Describe the pathophysiology and epidemiology of *Pneumocystis jirovecii* pneumonia (PJP)
2. Recognize steroid dose and duration thresholds that are associated with increased PJP risk
3. Outline literature and guideline recommendations to determine the need for PJP prophylaxis
4. Identify appropriate PJP prophylactic regimens and monitoring strategies

Outline

- Background information on PJP
- Prevalence and epidemiology of PJP within immunosuppressed patients
- Overview of immunosuppression related to steroids
- Prolonged steroid use
- Literature review
- PJP prophylaxis
- Key takeaways

Background Information

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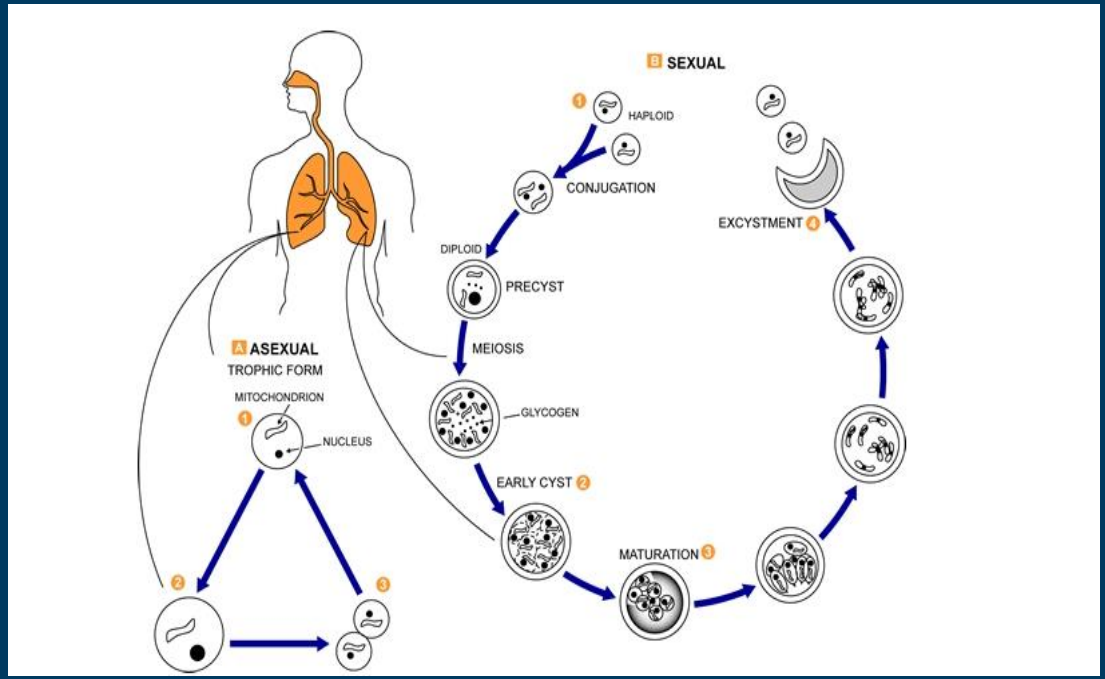
Pneumocystis jirovecii

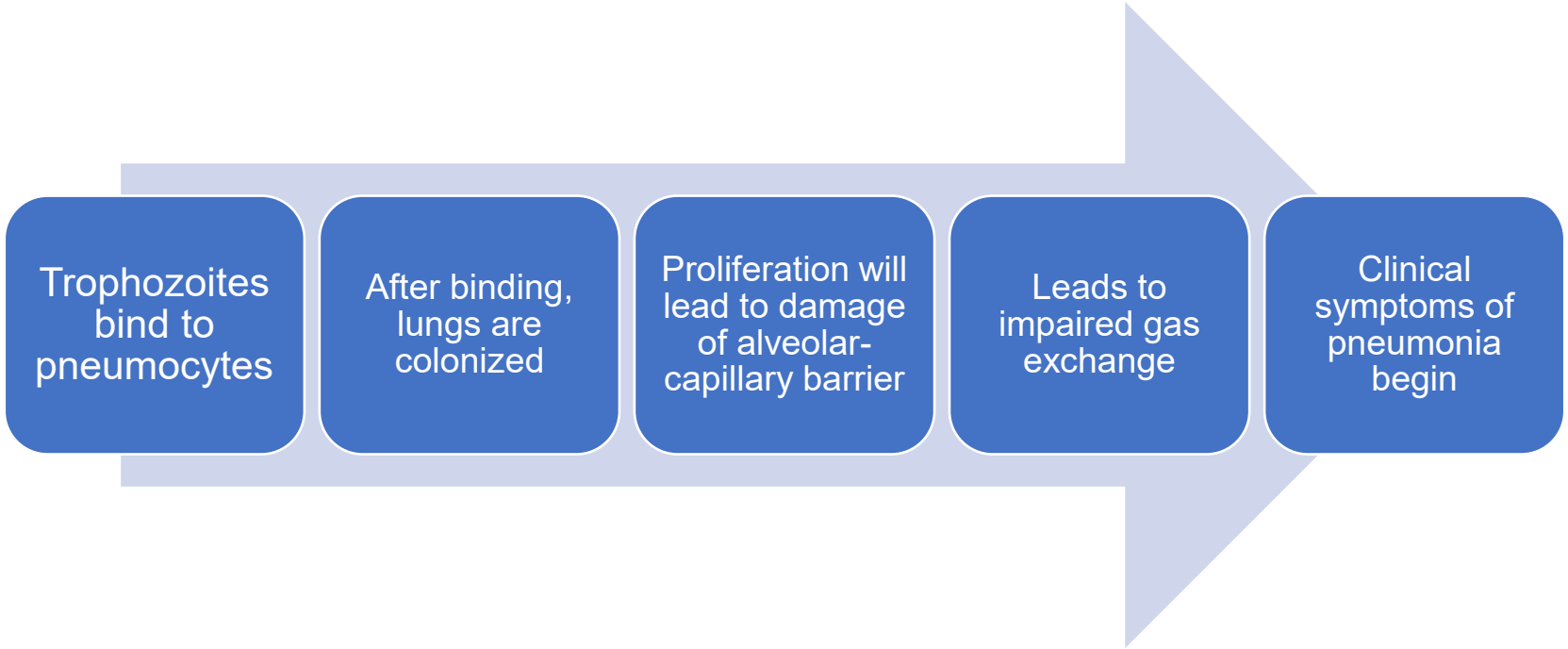
- Opportunistic fungal infection
- Found ubiquitously in nature
- Transmitted via airborne route

Fishman J, et al., J Fungi (Basel). 2022

Life Cycle of *Pneumocystis jirovecii*



Pathogenesis



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Fishman J, et al., J Fungi (Basel). 2022

Clinical Symptoms

- Non-productive cough
- Exertional dyspnea
- Crackles and rhonchi on auscultation
- Fever
- Hypoxemia
- Oral thrush
- Lactate dehydrogenase >500 U/L

Fishman J, et al., J Fungi (Basel). 2022
Pneumocystis pneumonia. HHS. HIV.gov
Pneumocystis jiroveciii pneumonia. NIH. NIH.gov

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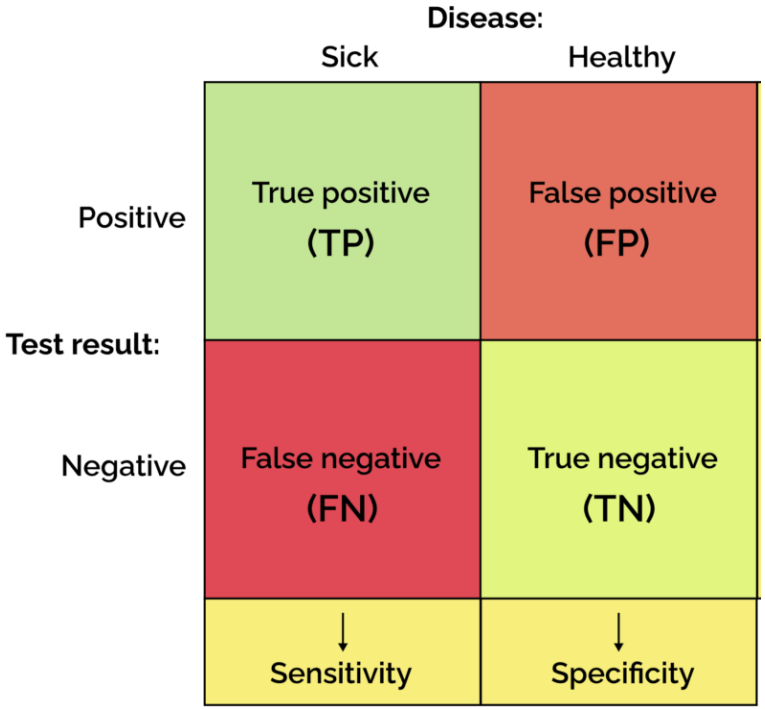
Sensitivity vs Specificity

Sensitivity

- The ability of the test to identify the presence of a disease or illness correctly

Specificity

- The ability of the test to identify the absence of a disease or illness correctly



GPExams. Sensitivity & Specificity. GPExams.com.

Diagnosis

Definitive diagnosis of PJP should be determined with histopathologic or cytopathologic demonstration of *Pneumocystis jirovecii*

Diagnostic Tool	Diagnostic sensitivity
Induced sputum	<50% - >90%
Bronchoalveolar lavage (BAL)	90% - 99%
Transbronchial biopsy	95% - 100%
Open lung biopsy	95% - 100%

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Fishman J, et al., J Fungi (Basel). 2022.
Pneumocystis pneumonia. HHS. HIV.gov

Sample Source

Serum

- 1,3-Beta-D Glucan Test (BDG)

Sputum or BAL

- Microscopic staining
- Polymerase chain reaction (PCR)

Fishman J, et al., J Fungi (Basel). 2022.
Babady N. E, et al., J Clin Microbiol. 2025

1,3-Beta-D Glucan Test

BDG: cell wall polysaccharide

- Found in the fungal cell wall of *Pneumocystis jirovecii*
- Released in the blood during active infection
- Detected via serum assay

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Fungitell STAT® Assay. Associates of Cape Cod, Inc.

BDG Test Performance

- High sensitivity for PJP
  - Often reported >90%
  - A negative BDG makes PJP unlikely
- Low specificity
  - Positive in other invasive fungal infections

Babady N. E, et al., J Clin Microbiol. 2025

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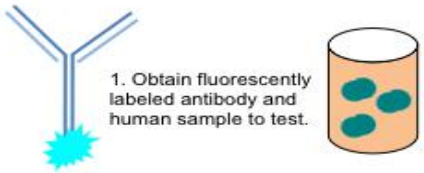
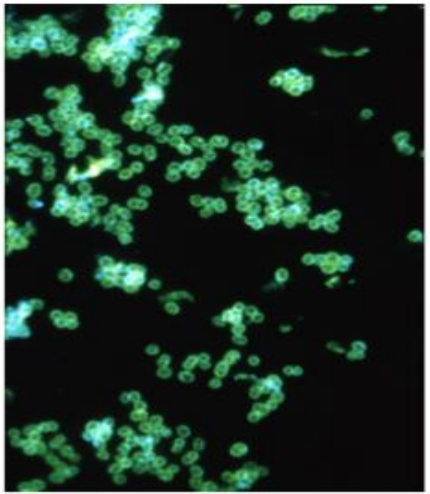
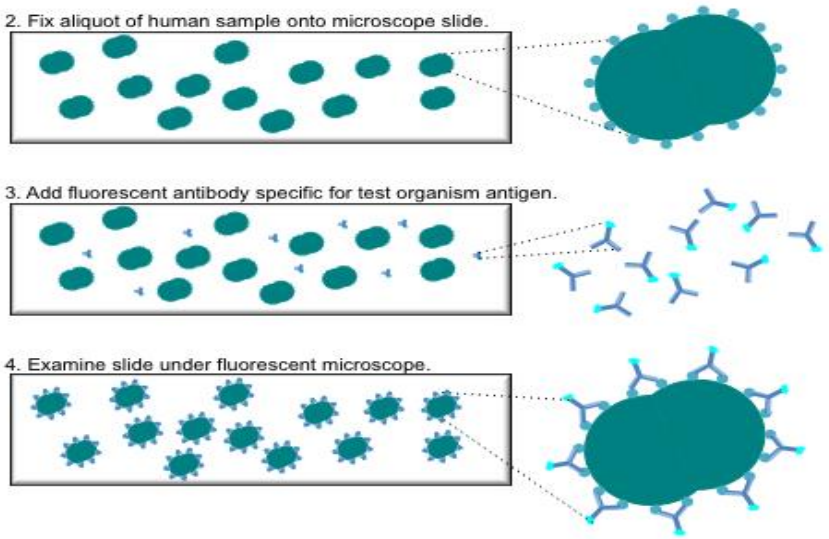
Microscopic Staining

Direct fluorescent antibody detection of bacteria in human sample



Example of fluorescent antibody staining of cell wall antigen of *Neisseria gonorrhoeae*. Courtesy of the Center for Disease Control and Prevention.





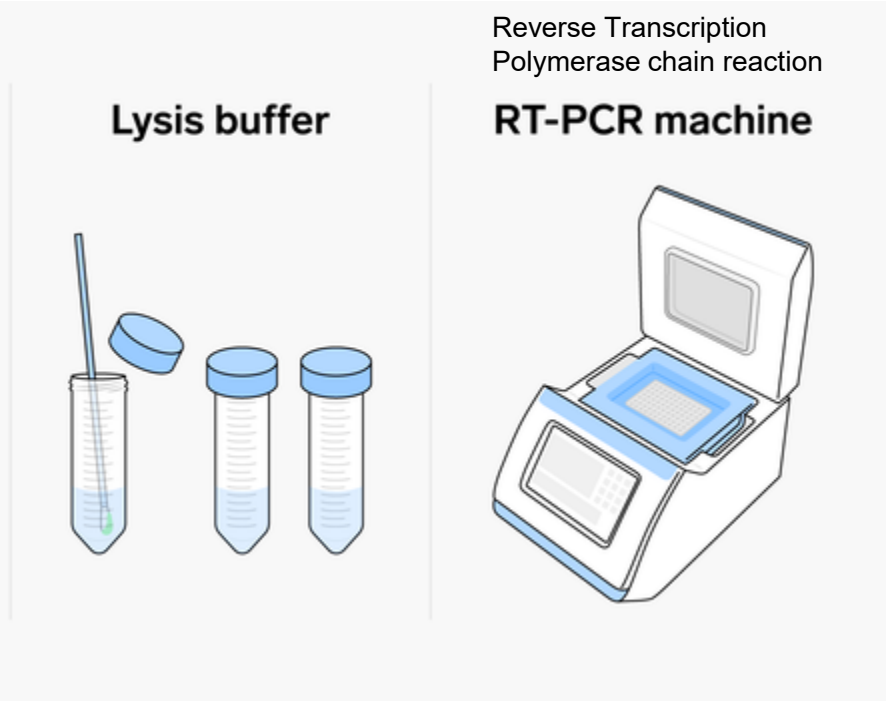
Babady N. E, et al., J Clin Microbiol. 2025

Microscopic Staining Limitations

- Variable sensitivity
  - Negative results are common, especially in:
    - Human Immunodeficiency Virus (HIV)-negative patients
    - Early or partially treated PJP
- Specimen type
  - BAL yields better detection
- Operator and technical variability
- Species life forms
  - Cysts only

Polymerase Chain Reaction

Reverse Transcription
Polymerase chain reaction



PCR Test Sensitivity

Very high sensitivity: 90–99%

- Superior to conventional microscopic staining, especially in:
  - Non-HIV patients
  - Patients receiving corticosteroids
  - Early or low-burden disease
- High sensitivity makes PCR useful as a **rule-out test**

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Babady N. E, et al., J Clin Microbiol. 2025

PCR Test Specificity

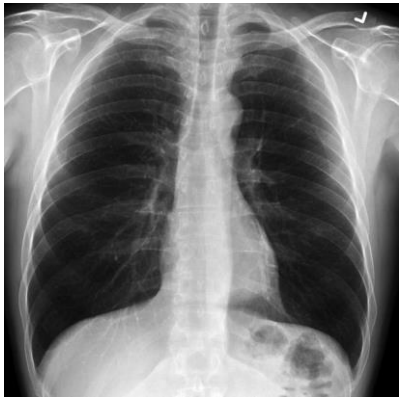
Moderate specificity: ~ 70–90%

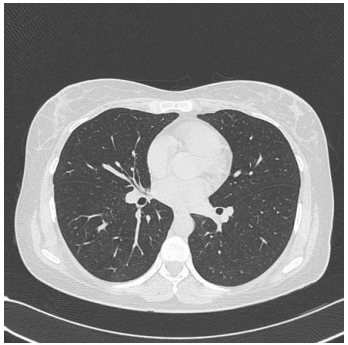
- Lower specificity compared to microscopy because PCR detects:
  - Active infection
  - Colonization
  - Residual deoxyribonucleic acid (DNA) from prior infection
- Specificity is particularly reduced in:
  - Chronic lung disease
  - Patients on prophylaxis
  - Intensive care unit (ICU) populations

Imaging

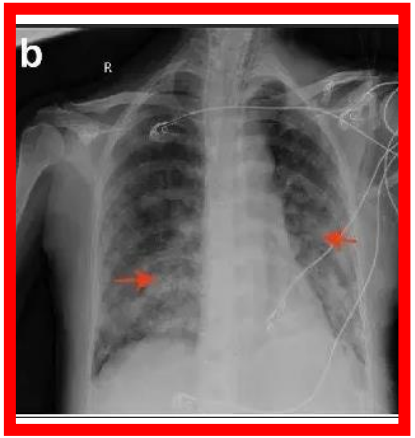
- Bilateral, diffuse interstitial infiltrates
  - Also described as opacities
  - Often symmetric
- Fine reticular or granular patterns
  - Shows alveolar and interstitial involvement

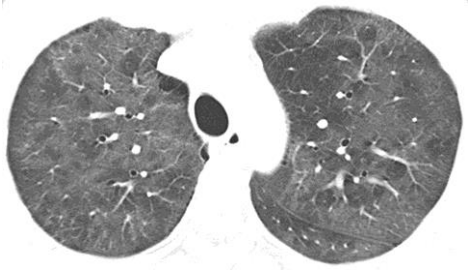
Normal





PJP





Babady N. E, et al., J Clin Microbiol. 2025
Pneumocystis pneumonia. HHS. HIV.gov
Gaillard F. Normal chest x-ray. Radiopaedia.org
Muzio, B. Normal chest CT. Radiopaedia.org
Kanne, JP, et al. PJP CT Findings. AJR. 2012

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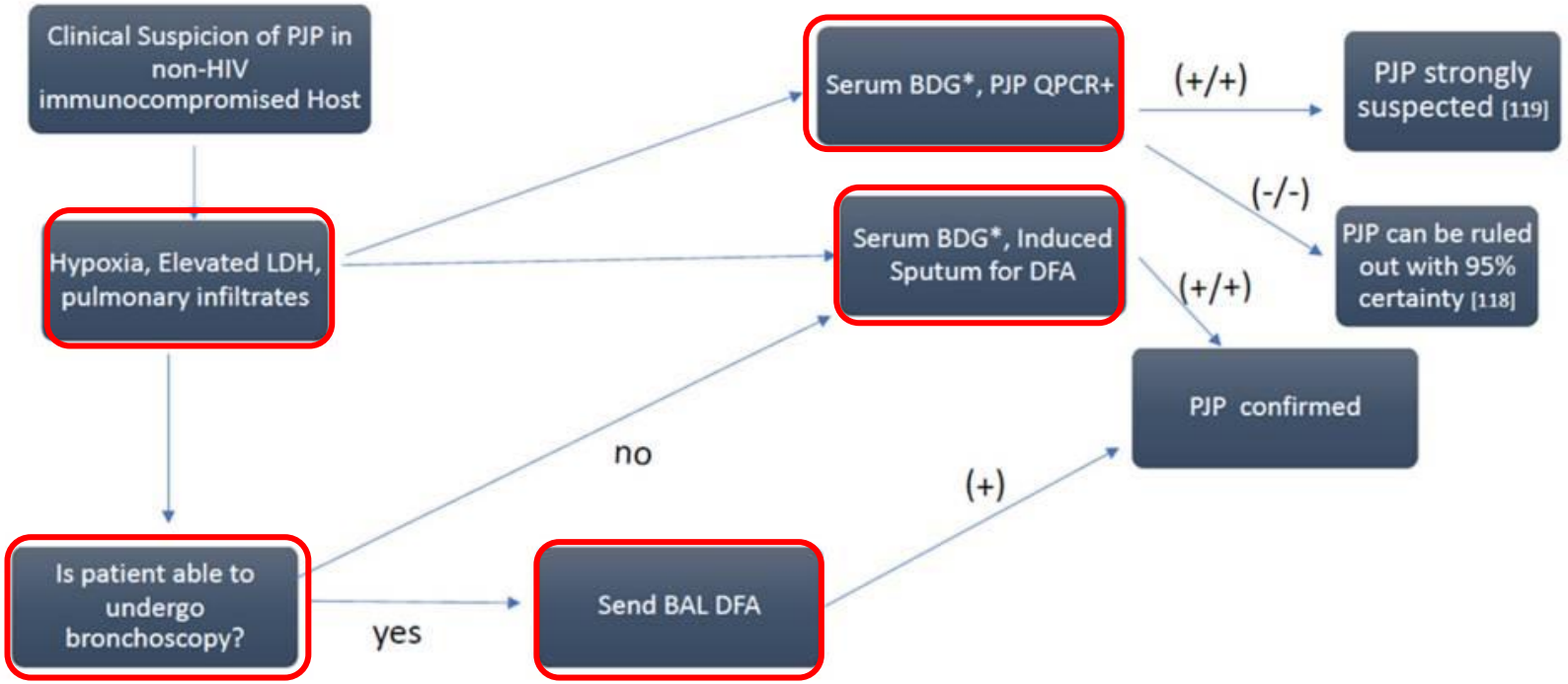
Approach to Diagnosis



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Fishman J, et al., J Fungi (Basel). 2022

Epidemiology of PJP and High-Risk Groups

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Epidemiology of PJP

- Historically associated with HIV
- Incidence in **HIV patients has declined** significantly due to:
  - Widespread antiretroviral therapy
  - Routine prophylaxis
- Incidence in **non-HIV immunocompromised patients has increased**
- Importantly, **non-HIV PJP is associated with higher mortality**, more acute presentations, and more frequent respiratory failure.

Quigley, N, et al. Open Forum Infect Dis. 2023

High Risk Populations

HIV infected patients

- Highest risk with
  - CD4 count <200 cells/mm^3
  - High viral load
- Now less common due to antiretroviral therapy (ART) and prophylaxis
- Clinical features:
  - Subacute onset
  - Higher organism burden

High Risk Populations

Patients Receiving Prolonged Steroids

- Corticosteroids are present in 80-90% of non-HIV PJP cases
- Longer duration of steroids puts a patient at higher risk

Malignancy

- Common in
  - Acute leukemias
  - Lymphomas
  - Patients receiving chemotherapy
- HIGH mortality

Other Contributing Factors

- Combined Immunosuppressants: Risks rise significantly when corticosteroids are combined with other agents like methotrexate or tacrolimus.
- Specific Agents: Anti-tumor necrosis factor (TNF)-alpha agents and alemtuzumab can significantly increase risk.

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Sonthalia, S, et al. StatPearls Publishing; 2025

Overview of Glucocorticoids and Immunosuppression

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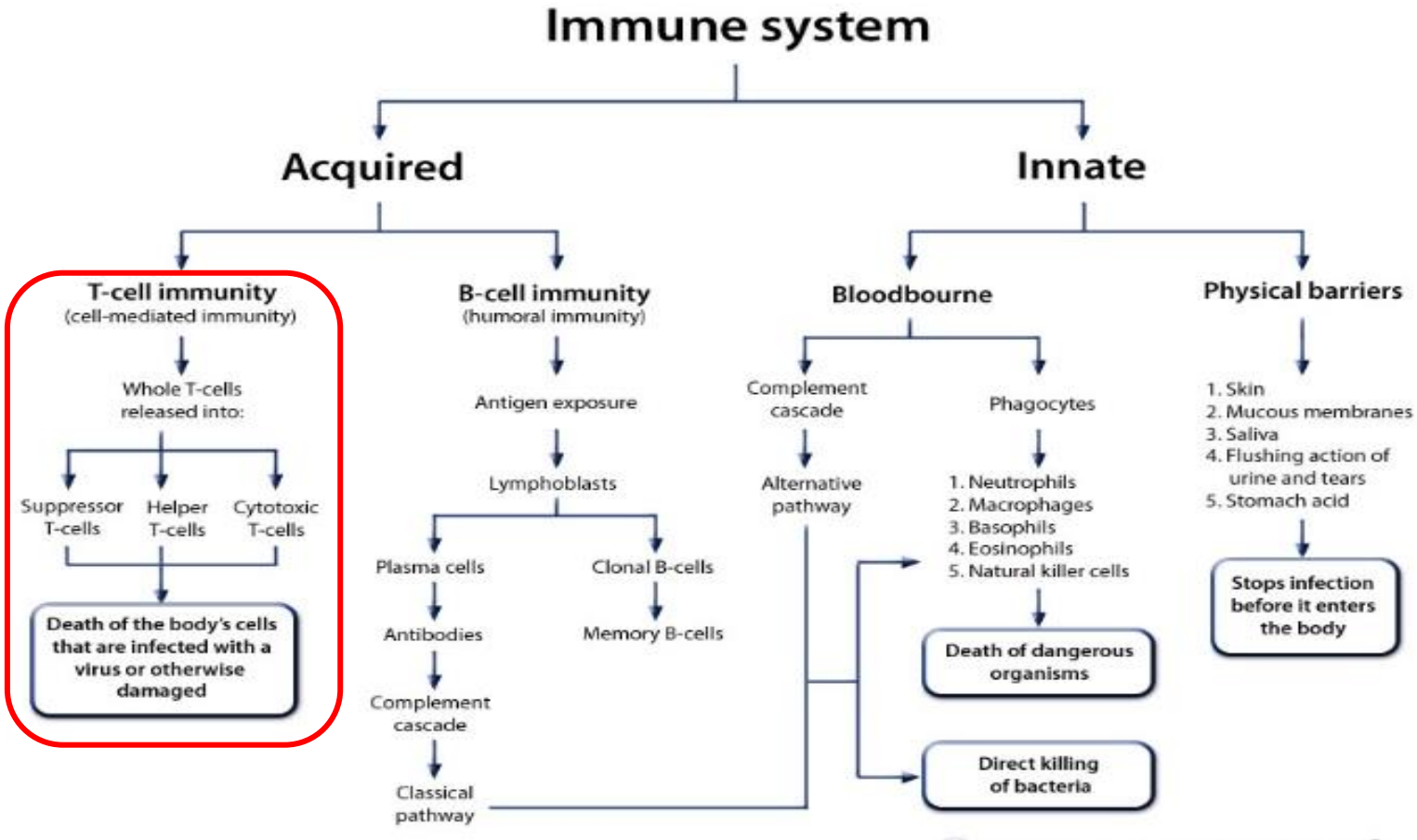

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Paul et al 2020 [5]

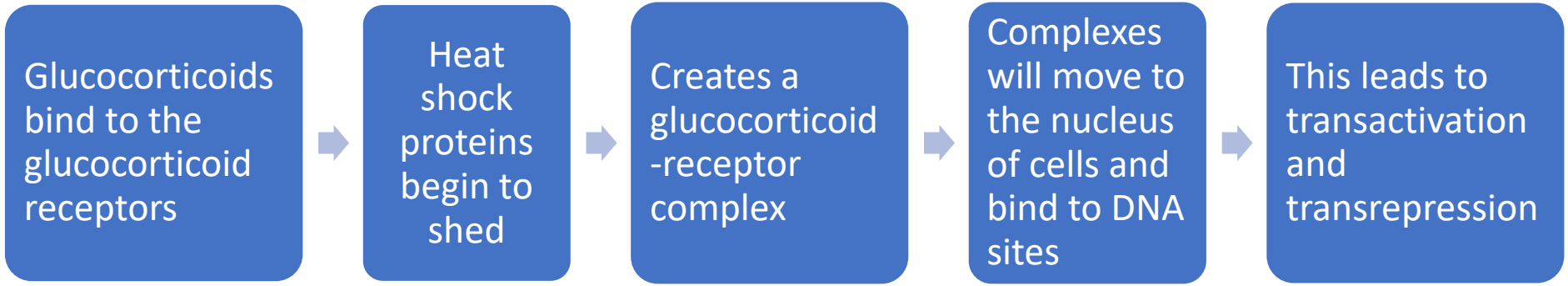
Glucocorticoids

- Glucocorticoids are steroid hormones secreted by the adrenal glands
  - Important for the maintenance of basal and stress-related homeostasis
  - Glucocorticoids affect cells by binding to the glucocorticoid receptor

- Glucocorticoids are widely used for the treatment of inflammation, autoimmune diseases, and cancer

Simeoni L. et al, Cell Commun Signal. 2025

Glucocorticoid Receptors



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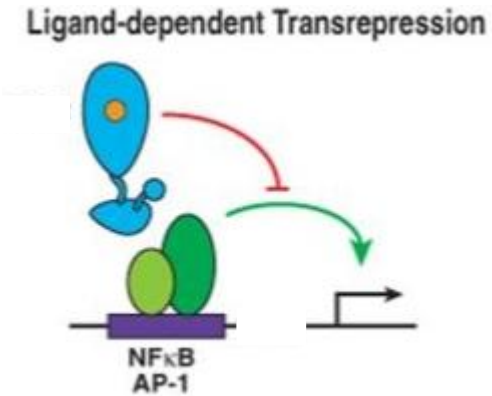
Simeoni L. et al, Cell Commun Signal. 2025.

Transrepression

Defined as: suppression of genomic transcriptions

Complexes cause suppression of:	Results in suppression in synthesis of proinflammatory cytokines:
• Nuclear factor -κB [NF-κB] • Activator protein-1 • Interferon regulatory factor-3	• Interleukins: IL-1, IL-2, IL-6, IL-8,tumor necrosis factor (TNF), Interferon(INF)-gamma, cyclooxygenase(COX)-2, vascular endothelial growth factor (VEGF), and prostaglandins



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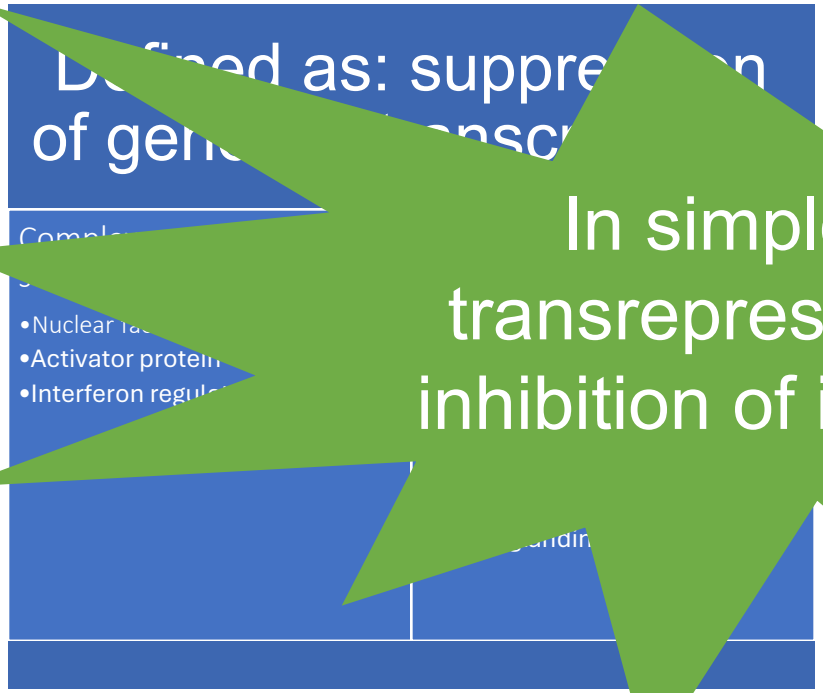
Simeoni L. et al, Cell Commun Signal. 2025

Transrepression



In simpler terms
transrepression means
inhibition of inflammation

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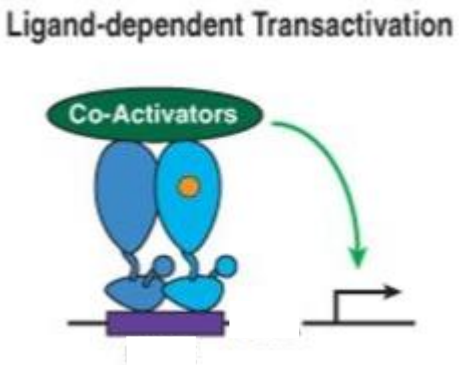
Simeoni L. et al, Cell Commun Signal. 2025

Transactivation

Defined as: activation of certain genomic transcriptions

Complexes cause activation of the synthesis of anti-inflammatory cytokines such as

- IL-10, NF-κB inhibitor, and lipocortin-1



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Simeoni L. et al, Cell Commun Signal. 2025

Transactivation

- IL-10, NF-κB inhi
  1

In simpler terms transactivation means upregulation of anti-inflammation

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Simeoni L. et al, Cell Commun Signal. 2025

Immunosuppression

- Inhibition and upregulation of certain genes in the synthesis of certain cytokines leads to:
  - Suppression of immune-mediated lysis
    - For PJP: Blocks the host immune system's ability to kill the organisms, allowing the fungus to colonize the lungs in large numbers and cause severe disease
  - Impaired immune cell function
    - Impede the access of these immune cells to inflammatory sites and suppress phagocytosis

Simeoni L. et al, Cell Commun Signal. 2025

Assessment Question #1

Which of the following best explains how systemic glucocorticoids increase the risk of opportunistic infections such as *Pneumocystis jirovecii* pneumonia (PJP)?

A. Enhancement of neutrophil oxidative burst and phagocytosis
B. Inhibition of B-cell antibody production leading to hypogammaglobulinemia
C. Inhibition of cytokine signaling required for macrophage-mediated pathogen clearance
D. Inhibition of B-cells and antibodies

Prolonged Steroid Use

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What is prolonged steroid use?

- Common threshold cited across studies:
  - ≥20 mg prednisone or prednisone equivalent/day for ≥4 weeks
  - >30 mg prednisone equivalent/day for > 4 weeks has also been cited as prolonged steroid use

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Li W, et al. Infect Drug Resist. 2025

Defining Prolonged

Study	Population	Dose (Prednisone Eq.)	Duration	Key Finding
Yale 1996	Non-HIV immunocompromised	≥20 mg/day	≥4 weeks	91% of PJP pts had recent steroid exposure; **established ≥20 mg × ≥4 weeks as common risk pattern**
Park 2018	Rheumatic diseases	≥30 mg/day	≥4 weeks	High-dose steroids ↑ PJP risk; prophylaxis significantly reduced incidence
Winthrop 2013	Rheumatoid arthritis + biologics	Dose-dependent	Not fixed; cumulative exposure	Higher prednisone dose independently ↑ opportunistic infection risk (incl. PJP)
Li 2019	Lung cancer pts	≥20 mg/day	≥3 weeks	Prolonged high-dose steroids independently associated with PJP development

Yale SH, Limper AH. Mayo Clin Proc. 1996
Park JW, et al. Ann Rheum Dis. 2018
Winthrop KL, et al. Arthritis Rheum. 2013
Li MC, et al. Sci Rep. 2019

Steroid Equivalence

Prednisone 20 mg PO Equivalence

- Prednisolone 20 mg PO
- Methylprednisolone 6 mg PO
- Dexamethasone 3 mg PO
- Betamethasone 3 mg PO
- Hydrocortisone 80 mg PO

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Yasir M, et al. StatPearls Publishing; 2025

Assessment Question #2

In which patient scenario should PJP prophylaxis be initiated?

A. Patient with osteoarthritis receiving 20 mg of intermittent triamcinolone intra-articular injections

B. Patient with dermatitis on topical triamcinolone for 7 days

C. Patient with rheumatoid arthritis receiving prednisone 25 mg PO daily for 6 weeks

D. Patient receiving a 5-day course of prednisone 50 mg PO daily for bronchitis

Overview of Guideline Recommendations for Rheumatological Diseases

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Guideline Recommendations for Autoimmune Inflammatory Rheumatic Diseases (AIRD)

- Consider prophylaxis for PJP in high-risk glucocorticoid use:
  - No threshold defined:
    - Prednisone (or equivalent) >15-30 mg PO for >2-4 weeks proposed
  - This recommendation applies especially when glucocorticoids are used in combination with other immunosuppressants

- European Alliance of Association for Rheumatology (EULAR) endorses trimethoprim-sulfamethoxazole (TMP-SMX) for certain rheumatic subgroups
  - Patients with Anti-Neutrophil Cytoplasmic Antibody (ANCA)-associated vasculitis receiving high-dose glucocorticoids, cyclophosphamide, and/or rituximab

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Limper AH, et al. Mayo Clin Proc. 1996

Overview of Guideline Recommendations for Solid Organ Transplant and Hematological Malignancies

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Guideline Recommendations in Solid Organ Transplant (SOT) Recipients

- **Why SOT patients are high risk**
  - Profound T-cell immunosuppression from induction agents (anti-thymocyte globulin (ATG), alemtuzumab)
  - Chronic maintenance immunosuppression (calcineurin inhibitors, mycophenolate mofetil (MMF), steroids)
- **Universal PJP prophylaxis recommended for all SOT recipients**
  - **Duration:**
    - Kidney, liver, heart: **6–12 months**
    - Lung, small bowel: **≥12 months or lifelong**
  - **Extended prophylaxis** recommended for:
    - Treatment of acute rejection
    - Prolonged high-dose steroids
    - CMV infection

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Fishman JA. *Clin Infect Dis.* 2019

NCCN Guideline Recommendations in Hematological Malignancies

- Immunosuppression caused by:
  - Cytotoxic chemotherapy
  - Prolonged corticosteroids
  - Targeted or biologic agents (e.g., purine analogs, anti-CD20 therapy)
- Patients receiving:
  - **Prolonged corticosteroids** (≥20 mg prednisone/day for ≥4 weeks)
  - **Purine analogs** (fludarabine, cladribine)
  - **Anti-CD20 therapy** (rituximab), especially with steroids
  - **Alemtuzumab**
- **Duration**
  - During active chemotherapy and
  - Continue until **immune recovery** (e.g., CD4 >200 cells/μL or ≥3–6 months post-therapy)
  - Hematopoietic Stem Cell Transplant (HSCT): typically, **6–12 months**, longer with chronic graft-versus host disease (GVHD)

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NCCN. Prevention and Treatment of Cancer-Related Infections. 2023

Summary of Evidence

- Very few randomized controlled trials specifically defining steroid-only prophylaxis thresholds
- Consistent observational data shows:
  - Dose ≥20 mg prednisone/day
  - Duration ≥4 weeks
  - Markedly increased PJP risk
  - Mortality higher in non-HIV patients → prevention critical

Limper AH, et al. Mayo Clin Proc. 1996
Fishman JA. *Clin Infect Dis.* 2019
NCCN. Prevention and Treatment of Cancer-Related Infections. 2023

Assessment Question #3

According to the 2022 EULAR recommendations, which scenario most strongly supports initiating PJP prophylaxis in a patient with autoimmune inflammatory rheumatic disease (AIRD)?

A. Prednisone 10 mg/day PO for 12 weeks with methotrexate

B. Prednisone 20 mg/day PO for 4 weeks with no other immunosuppression

C. Prednisone 25 mg/day PO for 6 weeks plus rituximab

D. Prednisone 30 mg/day PO for 7 days during disease flare

PJP Prophylaxis

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When to Consider Initiating PJP Prophylaxis

Consider prophylaxis if:

- Prednisone ≥20 mg/day (or equivalent) for ≥4 weeks OR
  - Malignancy
  - Transplant
  - Autoimmune disease
  - Concomitant immunosuppressants
  - Lymphopenia (CD4 <200 cells/mm³)

Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV. 2020.

First-Line Prophylaxis Option

- Trimethoprim-Sulfamethoxazole (TMP-SMX)
- Dosing
  - Double strength (DS): 800 mg/160 mg
  - Single strength (SS): 400 mg/80 mg
  - Immunocompromised host
    - Preferred regimens: 1 DS tablet PO once daily or 1 SS tablet PO once daily
    - Alternative: 1 DS tablet PO 3 times weekly

Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV. 2020.

TMP-SMX

- Mechanism of Action: Sequential inhibition of folate synthesis:
  - Sulfamethoxazole: inhibits dihydropteroate synthesis
  - Trimethoprim: inhibits dihydrofolate reductase
  - In combination results in bactericidal effect
- Adverse effects:
  - Common: Rash, gastrointestinal upset, photosensitivity
  - Serious: Stevens-Johnson Syndrome (SJS), bone marrow suppression, hyperkalemia, acute kidney injury (AKI)
- Contraindications:
  - Sulfa allergy, pregnancy (1st trimester and near term), severe hepatic disease
- Drug-Drug Interaction:
  - Methotrexate, warfarin, angiotensin converting enzyme/angiotensin receptor blockers (ACE/ARBs)
- Renal Adjustments
  - Creatine clearance (CrCl) 15-30 mL/min: reduce dose by 50%
  - CrCl <15 mL/min: avoid

Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV. August 18, 2020.

Reduction of *Pneumocystis jirovecii* pneumonia and bloodstream infections by trimethoprim–sulfamethoxazole prophylaxis in patients with rheumatic diseases

- **Population**
  - **Total patients:** 437 hospitalized adults with rheumatic diseases
  - **Inclusion:** Initiation of **high-dose corticosteroids**
  - **Follow-up window:** 4 months from steroid start
- **Intervention Groups**
  - **Prophylaxis group:** 376 patients received TMP/SMX
  - **Control group:** 61 patients did **not** receive TMP/SMX
- **Primary outcomes**
  - **PJP incidence**
  - **Non-central line associated bloodstream infections (BSIs)**

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Honda N, et al. Scand J Rheumatol 2021

Results

Outcome	TMP-SMX Prophylaxis	No Prophylaxis	Effect Estimate	95% Confidence Interval (CI)	Interpretation
Pneumocystis jirovecii pneumonia (PJP)	0 cases	3 cases	OR = 0.00	0.00–0.38	TMP-SMX prophylaxis was associated with a near-complete reduction in PJP; CI excludes 1 but reflects low event rate
Non–central line–associated bloodstream infections (BSIs)	Fewer events	More events	OR = 0.08	0.01–0.42	TMP-SMX prophylaxis significantly reduced odds of BSIs
TMP-SMX discontinuation	76 / 376 (20.2%)	N/A	—	—	One in five patients discontinued prophylaxis during follow-up

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Honda N, et al. Scand J Rheumatol 2021

Conclusions

- TMP-SMX prophylaxis significantly reduced the incidence of PJP
- Non–central line–associated bloodstream infections also decreased
- TMP-SMX prophylaxis may provide dual benefit:
  - Preventing both opportunistic fungal infection
  - Select bacterial infections during periods of intense immunosuppression

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Honda N, et al. Scand J Rheumatol 2021

Alternative Options

	MOA	Dosing	Adverse Effects	Clinical Pearls
Dapsone	Inhibits dihydropteroate synthase	100 mg PO daily	Hemolytic anemia, rash, nausea/vomiting	• Rule out G6PD deficiency Prior to initiation • No renal adjustments
Atovaquone	Inhibits mitochondrial electron transport by blocking cytochrome bc1 complex	1500 mg PO daily	GI upset, headache, rash	• Must be taken with food for absorption • No renal adjustments
Inhaled Pentamidine	Interferes with DNA, ribonucleic acid (RNA), phospholipid, and protein synthesis	300 mg via nebulization every 28 days	Bronchospasms, cough, wheezing, dyspnea	• Patient should be sitting upright • Can pre-treat with bronchodilators

Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents With HIV. 2020.

Assessment Question #4

Which prophylactic regimen is considered first-line for prevention of PJP in patients receiving prolonged high-dose corticosteroids?

A. Dapsone 100 mg PO daily
B. Atovaquone 1500 mg PO daily
C. Inhaled pentamidine 300 mg via nebulizer every 28 days
D. TMP-SMX 1 DS tablet PO three times weekly

Why is TMP-SMX First-Line?

- TMP-SMX has consistently been shown to be more effective at preventing and treating PJP than alternative agents, such as pentamidine, dapsone, and atovaquone
- It is the most well-studied and documented regimen for PJP management

Stern A, et al. Cochrane Database Syst Rev. 2014

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Duration for non-HIV immunocompromised Patients

- Continue until
  - Prednisone <15–20 mg/day PO or equivalent dose
  - Immune recovery
- Reassess during tapering
- Avoid premature discontinuation

Honda N, et al. Scand J Rheumatol 2021

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Duration for SOT Patients

- Continue ≥6 to 12 months
- During periods of increased immunosuppression
- Lifelong prophylaxis may be considered for high-risk recipients

Fishman JA. *Clin Infect Dis.* 2019

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Duration for HSCT Patients

- Continue through periods of significant immunosuppression
- For ~6 months in allogeneic HSCT recipients

Key Takeaways

Our Role as Healthcare Providers

- Identify patients on prolonged steroids
- Recommend prophylaxis initiation
- Monitor labs and adverse effects
- Educate providers on under-recognized risk
- Support antimicrobial stewardship

Conclusion

- Prolonged corticosteroid use is a major independent risk factor for PJP
- Observational studies consistently support the need for PJP prophylaxis at higher doses of steroids
- TMP-SMX prophylaxis significantly reduces PJP incidence
- Identifying non-HIV immunosuppressed patients can prevent high-mortality infections

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Questions?

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