Common Challenges and Mistakes in Managing and Preventing HIV-Associated Opportunistic Infections (OIs)

Mistakes/Learning Opportunities in Blue/Italics

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Disclosures: Allergan, Board
Learning Objectives

• Identify challenges and confounders in the diagnosis of opportunistic infections in HIV

• Recognize and manage common issues in the treatment of opportunistic infections in those with HIV
Annual Downloads of OI Guidelines 2000-2008

Dr. Henry Masur, personal communication
Improvement in Survival After AIDS OI in the ART Era

Survival remained poor with CNS lymphoma and JC virus encephalitis (PML)

Djawe et al, J Infect Dis 2015

5 year survivals

1997-2012  cART

1987-96  Mono/Dual ART

1981-6 pre- ART

Not Good Enough!

Survival remained poor with CNS lymphoma and JC virus encephalitis (PML)
Diagnose HIV Earlier, Before OI: Universal and Targeted Testing

CD4 Count at HIV Diagnosis US: 2000-2009

Buchacz K et al, HOPS study, AIDS Res Treat 2012
New OI Guidelines 2013*

Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

Centers for Disease Control (CDC), National Institutes of Health (NIH), HIV Medicine Association of the Infectious Disease Society of America (HIVMA of IDSA)


Mechanism to update recommendations regularly:
http://aidsinfo.nih.gov

*Published as Masur et al, Clin Infect Dis 2014. Abbreviated throughout my talk as “Guidelines”
Updates Since 2013 Include

- **Hepatitis B**: TAF/FTC (Descovy) included as a treatment option for patients with HBV/HIV coinfection.
- **FQ resistant Shigella**: FQ should only be used with *Shigella* isolates MIC<0.12 ug/ml
- **Pneumocystis jiroveci Pneumonia PJP or (PCP)**: criteria for stopping prophylaxis with CD4 100-200 and undetectable viral load
- **Cryptococcal meningitis (CM)**: No role for dexamethasone as adjunctive therapy
- **Human Herpesvirus 8 or HHV 8 (Kaposi’s Sarcoma Herpes Virus or KSHV)**. KSHV inflammatory cytokine syndrome (KICS) discussed. Treatment recommendations for multicentric Castleman's disease
Prevention of OIs is a Team Effort

• Physicians, NPs, PAs, RNs should utilize practice and hospital-based systems for
  • Screening and early detection
  • Preventive and vaccine strategies
  • Guidelines-based prophylaxis
• All practices should institute or upgrade efforts to audit and improve key quality measures in your specific population
  • Tools from population health initiatives
  • Role of electronic medical records
Early Diagnosis and Treatment of OIs Requires Multidisciplinary Collaboration

- Optimizing diagnostic testing strategies
  - Importance of the microbiology laboratory
- Monitoring of multiple and potentially overlapping drug toxicities
- Detection of drug interactions, with drug or dose adjustments
  - Collaboration with pharmacists
  - Role of OPAT (Outpatient Parenteral Antibiotic Therapy) programs
Patient 1: VT

- 44 y/o Vietnamese-American engineer (emigrated age 3), informed by phone of a positive HIV antibody test from an insurance physical
- Detailed history and exam normal
- CD4 258 (12%), HIV RNA 88,000 copies/ml
- Serologies: CMV (+), toxoplasma (-), VZV (-), RPR (-), Hep B sAb (+), Hep A IgG (+)
- PPD nonreactive, chest x-ray (CXR) clear
Patient 1: VT
You recommend

1. Do not start TMP/SMX (trimethoprim/sulfamethoxazole) prophylaxis for PCP*
2. Start TMP/SMX for prophylaxis

*Now Pneumocystis jiroveci pneumonia, which some people call PJP, I still call it PCP
You recommend:

- Do not start TMP/SMX (trimethoprim/sulfamethoxazole) prophylaxis for PCP*: 64%
- Start TMP/SMX for prophylaxis: 36%

Source:
CD4 Count and Risk of OI

CD4

Years After Infection

300

200

100

50

TB  PCP  CNS Crypto and Toxo  MAC  CMV

Phair et al, NEJM, 1990
25% of PCP Cases with CD4 >200

Rule of thumb: up to 25% of OIS not predicted by CD4 threshold

Primary Prophylaxis Guidelines: CD4 <200, CD4% <14%. Experts favor thrush and other OIs.
Understand Determinants of OI Risk Besides CD4

Epidemiology: including

- Geographic variability (prior colonization or infection)
- Vocation/avocation
- Immunizations
- Antibiotics or antifungals for other indications

- Malnutrition, steroids or other immunosuppression, pregnancy
- Lower CD4 nadir in previous year (especially <50)
- Recent or concurrent OI
- Higher HIV RNA
- Other host factors
Patient 2: CH

• 63 year old male admitted with myocardial infarction (MI), requiring pressors and intraaortic balloon pump (IABP)
• We are consulted for fever 101 and SOB
• History of 30 pound wt. loss in a year, rash, chest pain and dypsnea on exertion
  – Exam with inspiratory rales; treated for heart failure and community acquired pneumonia
• Arterial blood gas (ABG) 7.44/348/63 on 50% FI02
• Elevated lactic dehydrogenase (LDH) 262 (110-210)
• New Type 2 diabetes
CH Imaging and Course

- Induced sputum neg for PCP or bacterial infection
- SOB improves with diuresis
- Fever persists

Serum CrAg + 1:16
Lumbar puncture (LP) negative. You recommend:

1. Repeat induced sputum
2. Bronchoalveolar lavage (BAL)
3. Fluconazole treatment for cryptococcal disease
4. A plus C
5. B plus C

The GIGO Principle
Lumbar puncture (LP) negative. You recommend:

- Repeat induced sputum: 9%
- Bronchoalveolar lavage (BAL): 9%
- Fluconazole treatment for cryptococcal disease: 6%
- A plus C: 15%
- B plus C: 61%

Source:
Understand Operating Characteristics of Test Including Specimen Quality

- **High quality** “Induced” or endotracheal tube sputum: range of sensitivity “50-95%,” related to quality of specimen
  - Giemsa or Gomori methenamine silver (GMS) up to 80% sensitive
  - Direct fluorescent antibody (DFA) staining: up to 95% sensitive
- **Bronchoalveolar lavage with antibody staining:** 95-99% sensitive

- *Importance of deep specimen by good respiratory therapist, with coaching—assess adequacy and if inadequate specimen, repeat!*
Patient 3: JW

History and PE

- 47 year old truck driver (East, Midwest, West Coast) presents with 2 mos cough, DOE, SOB, fever and weight loss
- Shallow inspiration, inspiratory crackles 2/3 up L, ½ up R
- Thrush

Lab

- WBC 6, 12% L
- LDH 342
- CD4 9, HIV RNA 995,000 copies cc3
Patient JW Chest Imaging

[Images of chest X-ray and CT scans]
JW’s Pulmonary Disease Is Most Likely:

A. PCP alone
B. Bacterial pneumonia alone
C. PCP and bacterial pneumonia
D. Histoplasmosis
E. PCP and histoplasmosis
JW's Pulmonary Disease Is Most Likely:

- PCP alone: 18%
- Bacterial pneumonia alone: 1%
- PCP and bacterial pneumonia: 18%
- Histoplasmosis: 4%
- PCP and histoplasmosis: 60%

Source:
Recognize Early vs Late PCP

**Early**
- Subacute onset (3-6 weeks, mean 28 days)
- Dypsnea on exertion
- Shallow inspiration (restrictive defect)
- “Doorstop cough.” “What do you mean SOB?” “I feel like I can’t get air in, or take a deep breath, or catch my breath”
- $0_2$ sat and $p_02$ at rest normal
  - Desaturation with walking

**Late**
- SOB at rest
- Hypoxic at rest

- Cysts and trophs in alveoli
- Interstitial inflammation and progressive fibrosis
Lab Diagnosis of PCP

- Elevated lactic dehydrogenase (LDH): present in many tissues, including lung. MARKER OF INFLAMMATION
  - Very sensitive (over 90-95%) unless very early, so a normal LDH has excellent negative predictive value (NPV) for PCP in AIDS
  - However < 50% specific
  - Test at diagnosis and for response to treatment, IRIS, etc

- 1, 3-beta glucan: present in cell wall of fungi and PCP cysts: MARKER OF ORGANISM TITER
Patient JW—You recommend ART:

1. Day of PCP diagnosis
2. 1 week after PCP diagnosis
3. 2 weeks after PCP diagnosis
4. It depends
Patient JW—You recommend ART:

- Day of PCP diagnosis: 59%
- 1 week after PCP diagnosis: 2%
- 2 weeks after PCP diagnosis: 14%
- It depends: 25%

Source:
A5164: Early ART Reduced Risk of AIDS/Death
282 pts, median CD4 29

- Early (< 2 wks—median 12 days) vs deferred (> 4 wks) ART
- Reduced risk of death with early treatment

Zolopa et al, PLOS One, 2009
Individualize ART Initiation in PCP
≤14 days optimal, if stable

- Day 13: oxygen down to 2 liters, LDH declines to 269
- Day 14: starts ART
  - Steroid taper continuing
- Day 17: Worsening SOB, increased O2 requirement, LDH 320, 1,3 β-D-glucan unchanged
Immune Reconstitution Inflammatory Syndrome (IRIS)
“Paradoxical” IRIS:
Worsening of OIs Suspected or Diagnosed before ART
Remember “Paradoxical Worsening” of Infectious Diseases

- Patient gets worse on therapy before they get better: related to immune response to killing of organisms (antigen load)
  - Tuberculosis: CNS tuberculomas, pulmonary TB, lymphadenitis
  - Leprosy: worsening neuritis
  - HIV
  - Worsening of moderate or severe PCP
- HIV: Not only release of high level antigen, but also re-arming of the inflammatory response
  - TB, MAC, crypto, PML, KS
Paradoxical IRIS: Definition

A. New, worsening, or recurrent signs or symptoms consistent with an exaggerated or atypical inflammatory reaction to the previously diagnosed OI

AND

B. Exclusion of a new infection, a medication toxicity or other disease process as a possible cause of the worsening
Paradoxical IRIS: Definition

AND one of the following:

1. Localized skin or lymph node inflammatory manifestation on physical exam

2. Inflammatory manifestation or lesion on radiology (X-ray, CT, or MR imaging) or specialist exam (ophthalmology), or endoscopy

3. Histopathologic or cytologic evaluation of tissue or fluid consistent with inflammation, granulomas or necrosis
Paradoxical IRIS

- Highest incidence in TB, MAC, PCP, Crypto, KS, PML
- May be associated with:
  - Initially or persistently high antigen levels
  - Low CSF WBC count (cryptococcal meningitis)
  - Alterations in cytokine profiles (pro-inflammatory)
  - Differences in host immuno-genetics
- Possible treatment options:
  - Anti-inflammatories, analgesics
  - Corticosteroids
  - Extend/change treatment of OI
Patient JW

- Prednisone increased from 20 to 40 mg
- TMP/SMX course extended from 3-4 wks
- At 1 month of ART, viral load down to 546 copies; but CD4 also declines to 5 (but % up from 1.4 to 5.5%).
- Course complicated by recurrent pneumothoraces requiring chest tubes and talc pleurodesis
Patient JW

3 months after ART

- CD4 208
- R elbow erythema, pain and swelling with drainage
- Gram stain and bacterial culture negative
“Unmasking” IRIS: Inflammatory Presentations of Subclinical OIs

• Patients with preexisting high titer infection
  – Anergic so lack local or systemic signs or symptoms
• Most common in TB, DMAC, crypto, CMV (15-30%)
  – Average 4-12 wks after ART, but as short as 3-7 days and as long as 3-12 mos
• Prevention and early diagnosis are key (high level of suspicion for new presentation of infection with even early/minor clinical changes)
Patient 4: LM

- 46 y/o Zimbabwean woman
- 1 month altered MS, HA, blurred vision, hearing loss, lethargy
- In ED, afebrile, somnolent, arousable to touch, not to voice
- Mild nuchal rigidity, mild L hemiparesis
- HIV+
- LP: OP 55, glucose 36, total protein 34
- WBC 17
- Serum CrAg 1:4096
- CSF CrAg 1:8192
Benefit of Addition of FC, but not Fluconazole, to Ampho

- Randomized, 3 group, open label trial of induction therapy for crypto meningitis in HIV, conducted in Vietnam.
- 299 patients enrolled
- All patients received Ampho B 1 mg/kg/day
  - Group 1: 4 weeks Ampho B alone
  - Group 2: 2 weeks Ampho B plus FC 100 mg/kg/day: BENEFIT OVER AMPHO B
  - Group 3: 2 weeks Ampho B plus fluc 400 mg twice a day: NO BENEFIT OVER AMPHO

No Role for Routine Glucocorticoids, Even with Increased ICP

- Double-blind, randomized, placebo-controlled trial of CM in Vietnam, Thailand, Indonesia, Laos, Uganda and Malawi
- Dexamethasone (Dex) or placebo for 6 wks, with combination antifungal therapy
- Trial stopped for safety reasons when mortality 47% in Dex group vs 41% in placebo
  - Increased infections and adverse events in Dex group

IDSA Guidelines: Induction (Initial) Antifungal

• Symptomatic disease:
  – Lipid formulation 3-4 mg/kg/d preferred over Amphotericin B 0.7-1.0 mg/kg/d
    • Add 5FC 100mg/kg/d for initial 2 wks
  – Fluc 400-800 mg/d + 5FC or Fluc 1200 mg/d (both inferior to Ampho B based therapy)
• For mild, non CNS disease, fluc alone
• Asymptomatic infection, for example detected during work up of non CNS disease
  • Fluc 400-800 mg a day
IDSA Guidelines

“Consolidation” and “Maintenance

• Induction: “at least” 2 wks (until substantial clinical improvement and negative CSF culture
  – CSF and serum CrAg clear slowly
  – Low level +CrAg and low level positive India ink (even with rare budding yeast) can persist much longer (months to even years)
• Consolidation: 8 weeks of fluc 400 mg qd*
• Maintenance: fluc 200 mg qd

*Consider higher doses in high titer, longstanding, severe disease or aberrant treatment courses
Elevated ICP in CM

Clinical

• Present in 30-50% of pts
• Associated with higher rate of CN palsies and altered MS, as well as increased early mortality
• With reduction in ICP via drains or shunts, dramatic early and late improvement possible

IDSA Guidelines

• If OP > 25
  – Lumbar drainage sufficient to achieve closing pressure of < 20 or 50% of initial
  – Repeated drainage daily until opening pressure controlled and stable
• If elevated pressure persists
  – Lumbar drain or VP shunt
• We need to educate and enlist neurosurgeons in this treatment
Patient LW: ART Initiation

- Patient treated with induction with induction x 3 weeks
- Daily LPs then VP shunt

You recommend ART at
1. Time of CM diagnosis
2. 2 weeks after
3. 10 weeks after
4. Other
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Timing of ART in CM

- Early ART is associated with Crypto IRIS
- Crypto IRIS may be severe or fatal
- Uncontrolled studies favor deferred vs early
- Randomized, controlled clinical trial: COAT (Crypto Optimal ART Timing) Study
  - Early ART (7 to 11 days) vs deferred ART: 45% mortality vs 30% deferred
  - RR death 1.73 in early vs deferred therapy

Guidelines for ART Initiation in CM

- Consider between 2-10 wks
- Prudent to delay ART at least until after completion of antifungal induction (≥2 wks) and possibly until after induction/consolidation phase (≥10 wks)
- Delay in ART may be particularly important in those with evidence of increased ICP and low CSF WBC
- If ART started prior to 10 wks, be prepared to aggressively address IRIS
OIs in the US: Take Home Points

• Prevention is better than cure
  – To prevent OIs, do and teach universal testing, for earlier HIV diagnosis

• OIs have declined in those able to benefit from ART
  – Classical presentations still occur
    • Importance of understanding and applying principles of diagnosis and treatment from clinical trials
Take Home Points

• Beware “atypical” presentations
  – At higher CD4, particularly in the year after CD4 nadir <50-100
  – Unmasking or paradoxical IRIS

• New challenges:
  – Timing of ART initiation: individualize based on clinical features, site of infection, clinical and microbiologic response to treatment
  – Prevention, diagnosis and management of IRIS

• Particularly in CNS
Answers to Audience Response Questions
Patient 1: VT
You recommend

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2. Start TMP/SMX for prophylaxis
Patient CH

Lumbar puncture (LP) negative. You recommend:

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JW Pulmonary Disease Is Most Likely

A. PCP alone
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E. PCP and histoplasmosis
Patient JW: You recommend he start ART

1. Day of PCP diagnosis
2. 1 week after PCP diagnosis
3. 2 weeks after PCP diagnosis
4. It depends
Patient JW

3 months after ART

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Disseminated *Mycobacterium kansasii* infection with septic arthritis and osteomyelitis
Patient LW ART Initiation

• Patient treated with induction with induction x 3 weeks
• Daily LPs then VP shunt

You recommend ART at
1. Time of CM diagnosis
2. 2 weeks after
3. 10 weeks after
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