Challenges in Management of Opportunistic Infections
Lessons Learned 1991-2011

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“The patients who have done the best are those that have lived long enough to realize that my previous advice was incorrect.”

Brian Gazzard, M.D.

Vancouver AIDS Conference, 1996
Many Questions in Management of Ois have been Addressed by Controlled Clinical Trials
Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America

New guidelines in development: winter 2011 or spring 2012 predicted release date
Many Other Questions in Ois Are NOT Addressed by Controlled Clinical Trials
Patient JK

- 40 year old Congolese woman presents with 4 days of R abdominal pain
  - Exam shows a thin woman with low grade fevers and R lower quadrant tenderness without organomegaly or mass
- No other localizing or systemic signs or symptoms
- Past medical history
  - Sexual assault February 2010
  - G2P2, first child died in infancy.
  - Exploratory laparotomy for acute tubal disease 1995, details unavailable
- Pyuria and bacteruria on urine dipstick, treated for UTI without improvement
Patient JK: returns to Emergency Room

• Labs:
  – AST 55 (twice normal), ALT 28
  – Alkaline phosphatase 643 (5 times normal)
  – Albumin 2.8 (low), globulin 7.7 (high), CPK normal
  – WBC 7.2 (47P/30L/15M/8E), Hct 29 (MCV 76), plts 333. ESR 123
  – Urinalysis 3+ blood, 0-2 RBC, 3-5 WBC, few bacteria. Urine culture with few mixed bacteria

• Pelvic exam with R adenexal enlargement and tenderness, cervicitis
  – Cervical swab: negative for N. gonorrhea and chlamydia, moderate enteric gram negative rods
Patient JK--Imaging

Abdominal CT

Chest CT
Patient JK

- HIV antibodies: ELISA positive, later confirmed by Western Blot
- CD4 222, viral load 78,000 copies
Patient JK

• What is the cause of her tuboovarian abscess (TOA)?
  – Bacterial
  – Mycobacterial
    • Female genital tract TB common cause of infertility, less common cause of TOA
  – Other: ? Fungal, ? Other infectious or noninfectious
Patient JK

• What is the cause of her lung disease?
  – Miliary tuberculosis
  – Miliary fungal disease
  – Other infectious or noninfectious
Patient JK

• She complains of mild headache shortly after hospitalization, with no fever, nuchal rigidity or focal neurologic symptoms or signs
  – LP: opening pressure normal, glucose mildly low at 47, total protein mildly elevated at 57, CSF cryptococcal antigen positive at 1:2056, CSF culture with cryptococcus neoformans
Patient JK

- Sputum x 3 AFB stain and culture and fungal stain and culture negative
- Bronchoalveolar lavage for same studies negative
  - Up to 25% of those with miliary tuberculous lung disease will have negative sputum cultures
- Blood isolator cultures for TB negative
  - Blood cultures for cryptococcus positive
- ? Multiorgan disease due to disseminated cryptococcus, vs multiple infections

Sing Y et al, Intl J Gyne Path 2008; 27:37
Patient JK: How Sure is Sure Enough?

• Empiric treatment should consist of
  – 1. Antibacterial and antifungal treatment
  – 2. Antibacterial, antifungal and antimycobacterial treatment
“This is a second opinion. At first, I thought you had something else.”
How Broad is Broad Enough when Treating for OIs in AIDS?

Pros of “Covering Everything”
- Okum’s razor doesn’t apply so there is a reasonable likelihood there is more than one infection
- Avoid mortality (especially early mortality) while awaiting diagnostics
- No rapid diagnostics available
- No diagnostics available

Cons of “Covering Everything”
- Subjective intolerance
- Drug toxicity
  - Cutaneous drug reactions
  - End organ drug reactions
- Drug interactions
- Cost
Relationship between CD4 and clinical and pathological form of TB

Figure 1. Clinical and immunopathological courses of HIV-associated tuberculosis. The figure does not represent one patient but is a composite of cross-sectional data (Table 1).
Increased Incidence of Drug Reactions in the HIV-Infected in the US

• Adverse cutaneous drug reactions occur far more often in HIV-infected persons than in the general population
  – Most commonly morbilliform rash, followed by urticaria, followed by others including TEN
  – Most common drugs: TMP/SMX (up to 40%, up to half treatment limiting), penicillins, other
  – Rate of reactions increased as CD4 decreased
    • ? Detection bias

Coopman et al, NEJM 1993; 328:1070
Bigby M et al. JAMA 1986; 256:3358
Etiology of Increased Cutaneous Drug Reactions in AIDS

• Unlikely to be polymorphisms in drug metabolism

• “Immune dysregulation”
  – Increased rate of cutaneous drug reactions described in bone marrow transplant patients
  – In a retrospective review of patients treated for PCP with TMP/SMX, cutaneous reactions were more common in the subset NOT receiving corticosteroids (47% vs 13%)

• No patients had a treatment limiting cutaneous reaction while on steroids, 18% of those not on steroids did

Caumes et al, CID 1994; 18:319
ACTG 5164: Early (<2 week) vs Deferred (>2 week) ARV in Acute Ois Study Design

Zolopa A, et al. 15th CROI; Boston, MA (2008); Abst. 142.
ACTG 5164

- Majority of OI were PCP
  - Included ICU patients
  - MOST received corticosteroids for moderate to severe PCP
- TB was excluded from the study
- Median time to ARV initiation in “early” group was 12 days
- No difference between early vs delayed groups in primary, composite endpoint
A5164: Early ARV Associated with Reduced Risk of AIDS/Death

- No difference in rate of virologic suppression
- No difference in IRIS (10 immediate, 13 deferred)
- Conclusion: In this population, start ARV within 2 weeks
- CAN THIS BE GENERALIZED to NON PCP, NON STEROIDS?

Zolopa A, et al. 15th CROI; Boston, MA (2008); Abst. 142.
Patient JK

• Treated with
  – Ampicillin, gentamicin, metronidazole
  – Liposomal amphotericin (Ambisome) and 5-flucytosine
    • Pelvic pain and transvaginal ultrasound improved within 10 days
  – All cultures for tuberculosis remained negative over 6 weeks and she continued to improve

• Was it surprising that someone with a CD4 of 222 had probable widely disseminated cryptococcal disease?
CD4 Counts in HIV

- “Normal” counts form a bell shaped curve ranging from approximately 350 to 1500. General correlation with CD4%:
  - CD4 > 500: CD4% > 30%
  - CD4 200-500: CD4% 14-28%
  - CD4 <200 CD4% <14%

- CD4 calculated from 3 measured variables: WBC, % lymphocytes, % lymphocytes that are CD4+ (by FACS or fluorescent antibody cell sorting)
  - Large individual variability: 18% variability for CD4% and 25% for CD4 count
  - Rare instances of individuals or families whose CD4 epitopes are not recognized by the panel of monoclonal antibodies used in FACS
Distribution of PCP Cases by CD4 in the Multicenter AIDS Cohort Study (MACS)

Fully 25% of cases occurred above the “CD4 Threshold” of 200
Other Factors Impacting “Net State of Immunosuppression”

• Medications:
  – Corticosteroids or other bone marrow suppressive therapies
  – Chemotherapy
  – Interferon or PEG-Interferon

• Other Infections
  – HTLV-1 (Brazil, Caribbean, Japan)
  – Other viral infections including Hepatitis B and C, CMV, Epstein-Barr Virus

• Malnutrition

• Major medical illness or surgery

• Pregnancy (hemodilution)

• Sex, race, psychological or physical stress have little or no effect
Patient JK: Follow Up

- Hepatitis C antibody positive
- Treated with
  - Ampicillin, gentamicin, metronidazole
  - Liposomal amphotericin (Ambisome) and 5-flucytosine
    - Pelvic pain and transvaginal ultrasound improve within 10 days
    - Low grade fevers, alkaline phosphatase elevation and anorexia improve over many weeks
  - All cultures for tuberculosis remained negative over 6 weeks and she continued to improve
Patient JK: Conclusions

- CD4 count is the best surrogate marker for immunosuppression in AIDS, but is not a perfect predictor of OI risk
- Cutaneous drug reactions are common in AIDS, and may be prevented by corticosteroid use
- Consider whether there are good alternatives for treatment of the OI when you decide to incur the toxicity risks of starting early ARVs
Patient Mr. RL: 2005

- 46 year old man who presents for a yearly exam complaining of malaise, myalgias, weight loss, without fevers.
- Physical exam reportedly unremarkable
- Laboratories: Elevated hepatic transaminases at ALT 150s, AST 120s (6-8 times normal)
  - Denies a history of viral hepatitis or high risk behavior for viral hepatitis or HIV. Has 2-6 beers/week. No family history of liver disease.
  - Hep B sAg negative, sAb and cAb positive. Hep C Ab and RNA negative. Hep A Ab negative. Screen for hemachromatosis negative. ANA negative. AMA negative
Patient Mr. RL

- Liver biopsy with inflammation without fibrosis or other abnormalities, reported as “autoimmune hepatitis.”
- Patient begun on 60 mg of prednisone a day with remission of symptoms, weight gain, and over 2 months, normalization of hepatic transaminases
- Two attempts at slow prednisone taper failed when the patient got below 20 mg a day
Patient Mr. RL: 2006

- Progressive cough with scant sputum, dyspnea on exertion and one episode of hemoptysis
- Smoker, born and lived in Boston area his whole life, worked in sales, no known TB or other exposures
- Chest x-ray: large left upper lobe cavity with surrounding consolidation. CT confirms this and hilar lymphadenopathy
- Sputum studies unrevealing
- Left upper lobectomy performed and cultures grow Mycobacterium kansasii and mycobacterium avium complex (MAC)
Patient Mr. RL: 2006

• Infectious Disease consulted
• They note a history of odonophagia with oral candidiasis on exam
• Blood cultures for mycobacteria sent and turn positive 20 days later for mycobacterium avium complex (MAC)
• January 2007: HIV Ab test positive, HIV RNA 210,000 copies, CD4 2 (0.4%)
Patient RL: 2007

- Patient begun on fluconazole and TMP/SMX (Bactrim) prophylaxis
- Also begun on isoniazid, rifabutin, ethambutol and clarithromycin
- 2 days later, in the early morning, he is acutely ill with fever to 104, rigors, hypotension, lightheadedness and explosive watery diarrhea
  - Am cortisol <1.0, after cortrysyn stimulation, cortisol 8
<table>
<thead>
<tr>
<th>Type</th>
<th>Features</th>
<th>Incidence</th>
<th>Etiologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>ACTH independent</td>
<td>Prevalence: 40-110 cases/million</td>
<td>Autoimmune (70%-90% of cases in United States), frequently associated with a polyglandular deficiency syndrome</td>
</tr>
<tr>
<td></td>
<td>Adrenal gland dysfunction, destruction, or replacement; requires &gt;90% loss of adrenal tissue</td>
<td>Incidence: 6 cases/million per year</td>
<td>Infection</td>
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<td></td>
<td>Loss of mineralocorticoid and glucocorticoid production</td>
<td></td>
<td>HIV is the most common infectious cause in the United States</td>
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<tr>
<td></td>
<td>Increased ACTH production</td>
<td></td>
<td>AI develops in 30% of patients with advanced AIDS</td>
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<tr>
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<td>May be hyperpigmented</td>
<td></td>
<td>TB is the most common infectious cause worldwide</td>
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<td>Requires lifetime therapy</td>
<td></td>
<td>Inflammation</td>
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<td>Cancer (breast, lung, melanoma most common)</td>
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<td>Acute addisonian crisis</td>
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<td></td>
<td></td>
<td>Infectious (meningococcemia, purpura fulminans)</td>
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<td>Stress</td>
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<td></td>
<td>Hemorrhage (acute stress or anticoagulant-induced)</td>
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<td></td>
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<td></td>
<td>Shock</td>
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<tr>
<td>Secondary</td>
<td>ACTH dependent</td>
<td>Uncommon</td>
<td>Decreased or absent ACTH (may be panhypopituitary or anterior pituitary dysfunction)</td>
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<td></td>
<td>Signs and symptoms usually due to loss of glucocorticoid function</td>
<td></td>
<td>Pituitary depression, dysfunction/damage</td>
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<td>Usually have intact mineralocorticoid function</td>
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<td>Tumor, postpartum</td>
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<tr>
<td></td>
<td>Rarely hypovolemic, more commonly hypoglycemic</td>
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<tr>
<td>Tertiary</td>
<td>Due to hypothalamic/pituitary depression or absence</td>
<td>Most common form</td>
<td>Usually from iatrogenic corticosteroid therapy and suppression of the hypothalamic-pituitary-adrenal axis</td>
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<td></td>
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<td>Hypothalamic failure or dysfunction</td>
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*Data taken from references 2 and 12. ACTH indicates adrenocorticotropic hormone; HIV, human immunodeficiency virus; AI, adrenal insufficiency; AIDS, acquired immunodeficiency syndrome; and TB, tuberculosis.
Managing Adrenal Insufficiency

• Primary
  – Treat opportunistic infections, treat HIV

• Tertiary
  – Anticipate drug interactions before they occur
    • Rifampin and rifabutin upregulate glucocorticoid metabolism—increase dose and decrease interval of glucocorticoid treatment or replacement
    • Avoid ritonavir with fluticasone and other inhaled or topical steroids whose systemic levels are boosted, leading to steroid excess followed by adrenal suppression

• “Sick day” plan for medical stress

• Follow hypothalamic-pituitary axis (may take months or years to recover)

Patient RL

- Referred for HIV care
  - No additional history
  - Exam shows resolution of oral candidiasis

- Begun on Atripla (tenofovir, FTC and efavirenz) at first visit with us, about 3 weeks in mycobacterial treatment
Patient RL Viral Load and CD4

<table>
<thead>
<tr>
<th>Date</th>
<th>Viral Load</th>
<th>CD4</th>
<th>CD4%</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Jan 2007</td>
<td>220,000</td>
<td>2</td>
<td>0.4</td>
<td></td>
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<tr>
<td>June 2007</td>
<td>&lt;50</td>
<td>8</td>
<td>2</td>
<td>Prednisone taper begun</td>
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<tr>
<td>Jan 2008</td>
<td>&lt;50</td>
<td>24</td>
<td>3</td>
<td></td>
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<tr>
<td>June 2008</td>
<td>&lt;50</td>
<td>48</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Dec 2008</td>
<td>&lt;50</td>
<td>88</td>
<td>8</td>
<td>Off prednisone</td>
</tr>
<tr>
<td>June 2009</td>
<td>&lt;50</td>
<td>95</td>
<td>8</td>
<td></td>
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<tr>
<td>Dec 2009</td>
<td>&lt;50</td>
<td>102</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>June 2010</td>
<td>&lt;50</td>
<td>118</td>
<td>11</td>
<td></td>
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</tbody>
</table>
Patient RL: Clinical Course

• January 2009: low grade fevers, abdominal and low back pain, anorexia
Patient RL: Abdominal CT
Patient RL: Interventional radiology-guided biopsy of lymph node

H and E stain

Fite stain

Mycobacterial culture negative
Patient RL: necrotic mycobacterial lymph nodes near a growing abdominal aortic aneurysm

• 1. Mr. RL SHOULD get a course of corticosteroids
• 2. Mr. RL should NOT get a course of corticosteroids
Steroids in Mycobacterial Disease

– Mycobacterium leprae: treatment of neuritis (particularly paradoxical worsening on therapy in tuberculoid leprosy)

– Mycobacterium tuberculosis
  • Severe or worsening pleuro-pulmonary disease
  • Obstructing lymphadenopathy
  • TB pericarditis
  • TB meningitis and CNS tuberculoma

Paradoxical Worsening of TB

• FA: 38 year old Kuwaiti male with 1 yr hx progressive left sided numbness, speech arrest, headache.
• CT scan 2/99 with bilateral, multifocal, enhancing masses
• Rx dilantin, decadron. Declined biopsy and Rx stopped
• MGH 5/99. PMH:
  – 12/96 cervical and axillary LAD, bx negative
  – Childhood BCG, but PPD here + at >20 mm

Patient FA: 5/13/99 MRI
Patient FA

• Underwent stereotactic biopsy—loosely formed granulomas and no AFB on stain, TB later grew on culture

• Begun on 4 drug TB therapy with a 4 week dexamethasone taper
  – Felt better and did not return for follow up during the 4 weeks

• Just after taper completed, brought urgently to the ER with the worst headache of his life
Patient FA: Head CT 5/23/99
Patient FA

6/9/1999

5/13/1999
Corticosteroids in Immune Reconstitution Inflammatory Syndrome ("Paradoxical IRIS")

- No randomized, controlled trials yet completed
- Multiple case reports and small series
  - Differing underlying infections, TB predominates
  - Differing case definitions of IRIS
  - Differing steroid regimens
    - Usually reserved for severe IRIS, particularly CNS
- Symptomatic improvements reported
  - Some increased risk of other infectious and noninfectious complications with steroids in these and PCP trials
Patient RL: Clinical Course

- We opted not to treat with corticosteroids and his symptoms improved slowly, imaging even more slowly
- 2009: Arthralgias of large and small joints, R effusion with 40,000 WBC in fluid (90% PMNs) All stains and cultures negative.
  - Rheumatoid Factor now strongly positive
  - Responded to tap and one synovial triamcinolone injection and plaquenil
- “Rheumatoid IRIS!”
Patient RL: Conclusions

Think STEROIDS

Not THOSE steroids

– Think of adrenal insufficiency in patients with HIV
– Think about steroids when you consider timing of ARVs and timing of IRIS
– Think about whether to use steroids in IRIS
  • We need to understand risk for IRIS better
    – Immune genetics has been the key in some other infections with paradoxical worsening