Diagnostic Procedures for Pulmonary Infiltrates in the Compromised Host

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Eric Davis, MD - Pulmonary

Disclosure

Drs. Davis, Donowitz, and Douvas do not have any relevant personal or professional financial relationships to disclose
Dr. Michael Douvas: Introduction and case presentations

Learning Objectives

1. Review the differential diagnosis for pulmonary infiltrates in a compromised host

2. What are the diagnostic yields and complication rates for bronchoscopic procedures in an immunocompromised host

3. What are diagnostic alternatives/adjuvants to bronchoscopy in the workup of a febrile immunocompromised host with a pulmonary infiltrate
Case 1:
24 year-old woman originally from El Salvador who developed a persistent dry cough after completing 6 cycles of ABVD for Hodgkin lymphoma.

Case 2:
22 year-old woman in remission after completing treatment with R-EPOCH and high dose methotrexate for high risk diffuse large B cell lymphoma with CNS involvement with no symptoms and cavitating lesions found on restaging CT scan.
Case 3:
29 year-old man with history of substance abuse, incarceration, and recurrent peripheral T cell lymphoma with a fever and cough in the setting of neutropenia.

SETTINGS:
Congenital immunodeficiency
Acquired immunodeficiency – HIV
Autoimmune – RA
Solid organ transplant
Solid tumor – immunotherapy
Hematologic malignancy
Stem cell transplant
Differential Diagnosis:
Neoplasm/recurrence
Infection
  1. Viral
  2. Fungal
  3. Bacterial/septic emboli
  4. Mycobacterial
Inflammatory
  1. Drug induced
  2. Autoimmune
  3. Sarcoidosis
  4. Histiocytosis

Diagnostic Tests:
Serologic tests
  Fungal immunodiffusion
  Fungitell
  Quantiferon Gold
  Aspergillus antigen
Urine – Histoplasma antigen
Bronchoscopy - BAL
Biopsy
  Percutaneous
  Bronchoscopy
  VATS
Of the 60 bronchoscopies, 25 (41.6%) resulted in positive microbial data. 1 showed diffuse alveolar hemorrhage, for a total of 26 (43%) resulting in positive data. Of the 26 bronchoscopies with positive data, management was changed in 17 patients (65.3%).

Of the 60 bronchoscopies, 35 (57%) did not result in any microbial data. However, 3 of those 35 (8.6%), resulted in discontinuation of an antimicrobial agent, and thus changed management.

Overall, there was a change in clinical management in 20 of the 60 bronchoscopies, or 33.3% of the time.

6 minor complications including transient hypoxia, cough, and minimal bleeding. No major complications.

Dr. Gerald R. Donowitz: An ID perspective
Goals and Objectives of this Section of the “Chat”

1. Define the nature of the problem of pulmonary infiltrates in the compromised host.
2. Review the invasive procedures available to make a diagnosis.
3. Begin to develop a plan for what to do, and when to do it.

Pulmonary Infiltrates in the Compromised Host

25% of patients with profound (<300-500 pmn/mm³), prolonged (>10 days) neutropenia will develop pulmonary infiltrates.
Up to 60% of HSCT recipients will have pulmonary complications

Etiologies of Pulmonary Infiltrates In the Compromised Host

- Pulmonary infiltrates
  - infection
  - drug effect
  - underlying disease
  - disease-related

Infectious Etiologies of Pulmonary Infiltrates in the Compromised Host

<table>
<thead>
<tr>
<th>Gram-positive bacteria</th>
<th>Gram-negative bacteria</th>
<th>Viruses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus pneumoniae</td>
<td>Pseudomonas spp. *</td>
<td>Influenza A/B viruses</td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>Klebsiella pneumoniae</td>
<td>Pneumococcal pneumonia</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>Escherichia coli</td>
<td>Human metapneumovirus</td>
</tr>
<tr>
<td>Mycoplasma spp.</td>
<td>Legionella pneumophila</td>
<td>Listeriosis</td>
</tr>
<tr>
<td>Rhodococcus equi</td>
<td>Achromobacter xylosoxidans</td>
<td>Rhodococcus equi</td>
</tr>
<tr>
<td>Actinobacteria</td>
<td>Enterobacter cloacae</td>
<td>Actinomyces</td>
</tr>
<tr>
<td>Neisseria meningitidis</td>
<td>Citrobacter spp.</td>
<td>Neisseria meningitidis</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>Neisseria gonorrhoeae</td>
<td>Neisseria gonorrhoeae</td>
</tr>
<tr>
<td>Pasteurella multocida</td>
<td>Haemophilus influenzae</td>
<td>Neisseria gonorrhoeae</td>
</tr>
<tr>
<td>Neisseria meningitidis</td>
<td>Klebsiella pneumoniae</td>
<td>Neisseria meningitidis</td>
</tr>
<tr>
<td>Neisseria meningitidis</td>
<td>Pseudomonas aeruginosa</td>
<td>Pseudomonas aeruginosa</td>
</tr>
<tr>
<td>Neisseria meningitidis</td>
<td>Staphylococcus aureus</td>
<td>Neisseria meningitidis</td>
</tr>
</tbody>
</table>

*Particular risk for antimicrobial resistance, depending on local exposure patterns.

Case in Point

47 year old female with Stage 1 breast cancer recently completing 4 cycles of cytox/adria.
9/16: develops headache, fever, productive cough;
   ANC >3,000;
   lymphocytes .27k/µl
   CT as shown
Case Cont’d

Differential: CAP
- PJP (beta-D-glucan=300);
- legionella
- fungi (histo, blasto, asperg; see beta-D-glucan)
- cytoxan

Case Continued Some more

Bronchoscopy after 5 days of cefepime therapy and still febrile; no growth

Amphotericin started
Clinical Challenges of Pulmonary Infiltrates in the Compromised Host

Differential is large, and infections are only one of the possibilities

If infectious, may be bacterial, fungal or viral

If infectious, may be polymicrobial in 15%\(^1\)

No empiric therapy can cover all the possibilities.....and initial inadequate therapy → higher mortality

Clin Infect Dis: 2007; 45:228\(^1\)
BAL In the Compromised Host: What is the Diagnostic Yield?

133 patients (150 procedures)

60 pts HSCT  20 pts SOT  47 pts on chemo

5 pts misc

Diagnostic Yield of BAL
(Retrospective Chart Review)

79/150 procedures were diagnostic 52.6%

Viral  Bacterial  IPA  PCP  Fungal  Misc

48.1%  11.4%  17.7%  7.6%  7.6%  7.6%

44% significant findings
Standardized BAL Procedure in Cancer Patients
(Prospective Study)
n= 284
Heme Malignancy (57.2%)
solid tumors (31.7%)
misc (2.5%)

platelets>20,000; PO₂ > 90; nasal O₂ < 5L/min

Standardized BAL Procedure:
cont’d
BAL samples n=284
Heme n=187
No pathogen n=110 (58.8%)
Colonization/Contamination n=22 (11.8%)
Diagnostic n=55 (29.4%)

Non-Heme n=97
No pathogen n=45 (46.4%)
Colonization/Contamination n=11 (11.3%)
Diagnostic n=41 (42.3%)
Standardized BAL Procedure:
cont’d
Washing samples
n=269

Heme
n=177

No pathogen
n=77 (43.5%)
Colonization/Contamination
n=37 (21%)
Diagnostic
n=63 (35.5%)

Non-Heme
n=92

No pathogen
n=39 (42.4%)
Colonization/Contamination
n=30 (32.6%)
Diagnostic
n=23 (25%)

Bronchoscopy in Febrile Neutropenia
(Retrospective Chart Review)

26 pts F⁺, N⁺, CXR⁺

Diagnostic yield: 23%
× Candida: 17%
## Diagnostic Yield of BAL in Compromised Hosts

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Style</th>
<th>Patient Population</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ann Am Thorac Soc 2013(^1)</td>
<td>lit review</td>
<td>HSCT</td>
<td>42-65%</td>
</tr>
<tr>
<td>Cancer: 2011(^2)</td>
<td>prospective</td>
<td>n=284: heme/solid 57.2%/31.7%</td>
<td>29.4%/42.3%</td>
</tr>
<tr>
<td>Int Med J : 2011(^3)</td>
<td>retrospective</td>
<td>n=26 (febrile neutropenia) 73% heme malignancy</td>
<td>23%</td>
</tr>
<tr>
<td>Thorax(^4)</td>
<td>retrospective</td>
<td>n=95 heme malign (74% neutropenic)</td>
<td>42.9%</td>
</tr>
</tbody>
</table>

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## Bronchoscopy for the Compromised Host: So far we Know: Lesson 1

Yield is highly variable at 20-40%

Can be safely performed with platelets of 20-40,000 (no major bleeding noted in 74/98 patients with thrombocytopenia)\(^1\)

Diagnostic yield may be related to location in lung, nature of infiltrate, and symptoms.\(^2\)
Bronchoscopy for the compromised host: So far we know....cont’d

A higher diagnostic yield was demonstrated in patients whose predominant radiographic infiltrate is within the alveoli and airways, as compared to infiltrates were the abnormality is predominately extra-alveolar.

Ann Thorac Med:2013:8:153-159

Bronchoscopy for the compromised host: So far we know....cont’d

There is significantly higher diagnostic yield of bronchoscopy with bronchoalveolar lavage in the lower lobes than in the middle or upper lobes in the immunocompromised patients.

Ann Thorac Med:2013:8:153-159
Bronchoscopy for the compromised host: So far we know....cont’d

Immunocompromised patient with fever and chest symptoms have a higher diagnostic yield from fiber-optic bronchoscopy with bronchoaveolar lavage than symptomatic patients.

Ann Thorac Med: 2013:8:153-159

BAL for the Compromised Host: Lesson 2

Higher diagnostic yield with:
- tree-in-bud consolidation
- ground glass opacities

Lower diagnostic yield with:
- reticular-nodular infiltrates

( BAL biomarkers are helpful for diagnosis of aspergillus (sensitivity 49->90%) but need standardization )
Microbiology of BAL: Be a Little Wary: Lesson 3

<table>
<thead>
<tr>
<th>Diagnostic group</th>
<th>Specific etiology</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vital pneumonias' pneumonias</td>
<td></td>
<td>96</td>
<td>46.1</td>
</tr>
<tr>
<td>Plasmodium falciparum</td>
<td>9</td>
<td>11.4</td>
<td></td>
</tr>
<tr>
<td>Hemophilius influenza</td>
<td>9</td>
<td>11.4</td>
<td></td>
</tr>
<tr>
<td>Influenza A virus</td>
<td>5</td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td>Influenza B virus</td>
<td>4</td>
<td>5.1</td>
<td></td>
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<tr>
<td>H. influenzae</td>
<td>3</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>A H. parainfluenzae</td>
<td>2</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>M. pneumoniae</td>
<td>2</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Other bacterial pneumonias</td>
<td>9</td>
<td>11.4</td>
<td></td>
</tr>
<tr>
<td>Actinomycetes</td>
<td>9</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>2</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>A. mellitus</td>
<td>1</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>S. mutans</td>
<td>1</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>1</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>A. parainfluenzae</td>
<td>1</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>M. pneumoniae</td>
<td>0</td>
<td>0.0</td>
<td></td>
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<tr>
<td>Reinhold pneumonia aspergillosis</td>
<td>14</td>
<td>17.7</td>
<td></td>
</tr>
<tr>
<td>Other fungal pneumonias</td>
<td>0</td>
<td>0.0</td>
<td></td>
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<tr>
<td>Candida glabrata</td>
<td>2</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>C. guilliermondii</td>
<td>2</td>
<td>2.6</td>
<td></td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td>1</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>A. flavus species</td>
<td>1</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>M. tuberculosis</td>
<td>2</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>M. abscessus</td>
<td>2</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>A. whitei species</td>
<td>1</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>C. albicans</td>
<td>1</td>
<td>1.3</td>
<td></td>
</tr>
</tbody>
</table>

M. pneumoniae resist azithromycin

Ann of Thorac Medicine: 2013:8:153-158

BAL Microbiology: What to Believe?

- Mycobacteria
- PJP
- Legionella
- Bacteria—mostly enterococci
- coagulase-negative staph
- Fungi
- Candida—need histology
- Viruses
- CMV—need histology
Timing of Bronchoscopy: Important Lesson 4

598 patients with HSCT

- ≤4d: 73% yield
- ≥4d: 31% yield

Timing of Bronchoscopy: cont’d

<table>
<thead>
<tr>
<th>Yield</th>
<th>Time until Bronchoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>75%</td>
<td>24 hr</td>
</tr>
<tr>
<td>40%</td>
<td>5d</td>
</tr>
<tr>
<td>14%</td>
<td>≥ 10 d</td>
</tr>
</tbody>
</table>
So if Bronchoscopy Yields are So/So, What is Left To Do?

If obtaining tissue is the next step: what is the procedure to use?
- TBBx
- CT guided
- Open lung bx/VATS
TBBx in the Compromised Host

40 procedures in pts with heme malignancy

- **TBBx**: 55% dx yield
  - (14 dx added to BAL)
  - side effects: 2.5%

- **BAL**: 20% dx yield
  - (0 cases added to TBBx)

Benefit:
- 55-64% yield
- 7.6% increase over BAL
- only source of dx: 18% vs 86% non-diagnostic

Risk:
- bleeding, 2.5-31%
- pneumothorax

References:
So if Bronchoscopy Yields are So/So, What is Left To Do?

If obtaining tissue is the next step, what is the procedure to use?

- TBBx
- **CT guided**
- Open lung bx/VATS

CT-Guided Percutaneous Lung Biopsy in the Compromised Host

213 pts with heme malignancy undergoing CT guided bx for pul lesions

- 60 % specific diagnosis (53% with neg BAL, TBBx)
- 62.8% malignancy
- 34.2% infection

Hematol Oncol: 2010; 28: 75-81
CT guided Percutaneous Biopsy: cont’d

higher yields with:
lesions > 1 cm
cavity lesions
lung masses

lower yields with:
lesions < 1 cm
lung nodules
consolidation

CT Guided Percutaneous Biopsy

Complications:
Pneumothorax requiring a chest tube: 15%
So if Bronchoscopy Yields are So/So, What is Left To Do?

If obtaining tissue is the next step, what is the procedure to use?
- TBBx
- CT guided
- Open lung bx/VATS

Open Lung Biopsy in the Compromised Host

Retrospective study of open lung biopsy or VATS in patients with heme malignancy or HSCT

- 63 patients (67 procedures)
- 62% yield
  - inflam disorders 23%
  - infection 21%
  - malignancy 18%
Open Lung Biopsy in the Compromised Host

complication rate: 13%; (major 3%)

prolonged chest tube -7%
mechanical ventilation 7%

Fewer complications with platelets > 50,000

Importance of Lung Biopsy for Presumed Fungal Infections

In 31 cases with CT suggestion of aspergillus infection lung biopsy proved aspergillus in 53%. ¹

In patients with neutropenic fever, and abnormal CT(79% nodules,24.1% of which had a halo sign) bronchoscopy had a 12.8% yield, percutaneous lung biopsy a 35% yield, open lung biopsy, 100% yield²

¹Am J of Hematol:2002:71:75-79
²Mycoses:2011:54:59-70
The Compromised Host with Pulmonary infiltrates: A Plan

Stay Tuned...

Dr. Eric Davis: A pulmonary perspective
What are some diagnostic options for bronchoscopy?

ATS Video Lecture Series

https://www.youtube.com/watch?v=hK4nNF9Gt14

What is a trans-bronchial biopsy?

ATS Video Lecture Series:
Perhaps I am overly concerned about the bleeding risk... I should stick with CPAP
I am not the only sleep specialist to tackle this question here at UVA...

**Deaths and Complications Associated with Fiberoptic Bronchoscopy**

*Paul M. Suratt, M.D.,** Joseph F. Smiddy, M.D.,† and Brian Gruber‡*

Survey data including over 1,000 questionnaires assessing 48,000 bronchoscopies and over 6,000 biopsies.

- 12 deaths were reported by 11 physicians
- 27 life threatening cardiovascular complications
- 52 life threatening airway complications

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**In general, complication rates for trans-bronchial biopsies are low**

Retrospective review of over 4,000 bronchoscopies including 2.5k BALs and 173 trans-bronchial biopsy procedures

- All patients had a platelet count of >60k and normal coagulation parameters if TBBx performed

<table>
<thead>
<tr>
<th>Complication</th>
<th>No.</th>
<th>% of FFBs</th>
<th>% Transbronchial Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumothorax</td>
<td>7</td>
<td>0.16</td>
<td>4</td>
</tr>
<tr>
<td>Pulmonary hemorrhage (&gt;50 mL)</td>
<td>5</td>
<td>0.12</td>
<td>2.8</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>11</td>
<td>0.2</td>
<td>...</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>0.55</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Pue, CA and Pacht ER. Chest 1995
What is the bleeding rate in a high risk, thrombocytopenic patient population?

- University of Michigan
- 24 patients with platelet count <60k over a 3 year period
- All had malignancy and/or recent chemo

<table>
<thead>
<tr>
<th>Patient</th>
<th>Platelet Count</th>
<th>Before TBI</th>
<th>After TBI</th>
<th>Complications</th>
<th>Bleeding Complications</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>7,000</td>
<td>6</td>
<td>11,000</td>
<td>0</td>
<td>Aspiration (THB)</td>
<td>Died</td>
</tr>
<tr>
<td>Case 2</td>
<td>10,000</td>
<td>6</td>
<td>11,000</td>
<td>0</td>
<td>Aspiration (THB)</td>
<td>Died</td>
</tr>
<tr>
<td>Case 3</td>
<td>12,000</td>
<td>6</td>
<td>11,000</td>
<td>Node hematoma</td>
<td>N/A</td>
<td>Died</td>
</tr>
<tr>
<td>Case 4</td>
<td>5,000</td>
<td>0</td>
<td>11,000</td>
<td>None</td>
<td>Micronucleation (THB)</td>
<td>Died</td>
</tr>
<tr>
<td>Case 5</td>
<td>10,000</td>
<td>6</td>
<td>11,000</td>
<td>BM clot</td>
<td>F-senso (THB)</td>
<td>Died</td>
</tr>
<tr>
<td>Case 6</td>
<td>10,000</td>
<td>0</td>
<td>11,000</td>
<td>None</td>
<td>N/A</td>
<td>Died</td>
</tr>
<tr>
<td>Case 7</td>
<td>10,000</td>
<td>0</td>
<td>11,000</td>
<td>None</td>
<td>N/A</td>
<td>Alive</td>
</tr>
<tr>
<td>Case 8</td>
<td>10,000</td>
<td>0</td>
<td>11,000</td>
<td>None</td>
<td>N/A</td>
<td>Alive</td>
</tr>
<tr>
<td>Case 9</td>
<td>30,000</td>
<td>0</td>
<td>11,000</td>
<td>None</td>
<td>N/A</td>
<td>Alive</td>
</tr>
<tr>
<td>Case 10</td>
<td>22,000</td>
<td>0</td>
<td>11,000</td>
<td>None</td>
<td>N/A</td>
<td>Alive</td>
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<tr>
<td>Case 11</td>
<td>22,000</td>
<td>0</td>
<td>11,000</td>
<td>None</td>
<td>N/A</td>
<td>Alive</td>
</tr>
<tr>
<td>Case 12</td>
<td>5,000</td>
<td>0</td>
<td>11,000</td>
<td>None</td>
<td>N/A</td>
<td>Died</td>
</tr>
<tr>
<td>Case 13</td>
<td>5,000</td>
<td>0</td>
<td>11,000</td>
<td>None</td>
<td>N/A</td>
<td>Died</td>
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<tr>
<td>Case 14</td>
<td>10,000</td>
<td>0</td>
<td>11,000</td>
<td>None</td>
<td>N/A</td>
<td>Died</td>
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<td>Case 15</td>
<td>10,000</td>
<td>0</td>
<td>11,000</td>
<td>None</td>
<td>N/A</td>
<td>Died</td>
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<tr>
<td>Case 16</td>
<td>10,000</td>
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<td>11,000</td>
<td>None</td>
<td>N/A</td>
<td>Died</td>
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<td>Case 17</td>
<td>10,000</td>
<td>0</td>
<td>11,000</td>
<td>None</td>
<td>N/A</td>
<td>Died</td>
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<tr>
<td>Case 18</td>
<td>10,000</td>
<td>0</td>
<td>11,000</td>
<td>None</td>
<td>N/A</td>
<td>Died</td>
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<tr>
<td>Case 19</td>
<td>10,000</td>
<td>0</td>
<td>11,000</td>
<td>None</td>
<td>N/A</td>
<td>Died</td>
</tr>
<tr>
<td>Case 20</td>
<td>10,000</td>
<td>0</td>
<td>11,000</td>
<td>None</td>
<td>N/A</td>
<td>Died</td>
</tr>
<tr>
<td>Case 21</td>
<td>10,000</td>
<td>0</td>
<td>11,000</td>
<td>None</td>
<td>N/A</td>
<td>Died</td>
</tr>
</tbody>
</table>

Papin TA et al. Chest 1985

21% with significant bleeding complications
4.2% fatality rate
What is the risk if we don’t get a diagnosis to help the patient, oncologist, ID colleagues?

- I am not here to say NO to any consideration of trans-bronchial biopsy in this patient population.

- My goal is to indicate a need to pause and consider if it truly adds an increased diagnostic yield to overcome the added risks of the procedure.

- Here is my brief data review

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Early study points to added value of trans-bronchial biopsies in febrile neutropenic patients

Pulmonary Infiltrates and Fever in Patients with Hematologic Malignancy

Assessment of Transbronchial Biopsy

- Prospective series of 43 patients with leukemia/lymphoma at BWH
- 14 patients had TBBx, 9 of which led to a diagnosis
- Note that BAL was not an option at that time

<table>
<thead>
<tr>
<th>Procedure</th>
<th>No. of Patient Procedures</th>
<th>Procedures Possible for Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum smear and culture</td>
<td>47</td>
<td>10</td>
</tr>
<tr>
<td>Bronchial washing</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Percutaneous needle aspiration of lung</td>
<td>4</td>
<td>2†</td>
</tr>
<tr>
<td>Fiberoptic bronchoscopy</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>Open-chest lung biopsy</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

* Bronchoscopically directed fiberoptic bronchoscopy procedures are not included.
† Cultures from one needle aspirate confirm spectrum results.
Selective use of trans-bronchial biopsies may improve diagnostic yield (particularly of non-infectious etiology)

- Prospective observational study 2004
- 104 consecutive non-HIV immunocompromised patients
- Sampling was determined by operator
- Primary outcome – diagnostic yield

Table 3—Sampling Procedures Performed During 104 FBs

<table>
<thead>
<tr>
<th>Sampling Procedure</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAL</td>
<td>99 (93.2)</td>
</tr>
<tr>
<td>TBB</td>
<td>45 (41.2)</td>
</tr>
<tr>
<td>RW</td>
<td>44 (42.3)</td>
</tr>
<tr>
<td>PSB</td>
<td>45 (42.4)</td>
</tr>
<tr>
<td>BAL + PSB</td>
<td>40 (37.9)</td>
</tr>
<tr>
<td>BAL + TBB</td>
<td>40 (35.5)</td>
</tr>
<tr>
<td>BAL + PSB + TBB</td>
<td>28 (27.3)</td>
</tr>
</tbody>
</table>


Selective use of trans-bronchial biopsies may improve diagnostic yield (particularly of non-infectious etiology)

- Complications occurred in 21% of patients.
- TBBx associated with higher complications.

Table 5—Diagnostic Yield of Sampling Procedures Performed During FB

<table>
<thead>
<tr>
<th>Sampling Procedure</th>
<th>Final Diagnosis</th>
<th>Diagnostic Yield of Sampling Procedurea</th>
<th>95% CI, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAL (n = 99)</td>
<td>125</td>
<td>109 (106.4)</td>
<td>98.5-116.3</td>
</tr>
<tr>
<td>RW (n = 44)</td>
<td>54</td>
<td>43 (97.7)</td>
<td>90.3-105.1</td>
</tr>
<tr>
<td>TBB (n = 49)</td>
<td>54</td>
<td>42 (85.3)</td>
<td>76.4-94.2</td>
</tr>
<tr>
<td>PSB (n = 45)</td>
<td>45</td>
<td>8 (11.1)</td>
<td>5.5-18.7</td>
</tr>
<tr>
<td>BAL + PSB (n = 40)</td>
<td>51</td>
<td>32 (63.9)</td>
<td>52.7-74.1</td>
</tr>
<tr>
<td>BAL + TBB (n = 44)</td>
<td>42</td>
<td>37 (88.1)</td>
<td>78.6-97.6</td>
</tr>
<tr>
<td>BAL + PSB + TBB</td>
<td>28</td>
<td>22 (78.6)</td>
<td>61.7-95.5</td>
</tr>
</tbody>
</table>

aDiagnostic yield for a sampling procedure is the ratio of diagnostic yielded by a sampling procedure or combination of sampling procedures (numerator) and all final diagnoses in patients undergoing these sampling procedures (denominator). Values given as No. (%).

Table 7—Exclusive Diagnosis by TBB (n = 17*)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>2</td>
</tr>
<tr>
<td>Radiation/chemotherapy induced pneumonitis</td>
<td>1</td>
</tr>
<tr>
<td>Wegner granulomatosis</td>
<td>2</td>
</tr>
<tr>
<td>Diffuse alveolar damage</td>
<td>4</td>
</tr>
<tr>
<td>ROP</td>
<td>1</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>4</td>
</tr>
<tr>
<td>Non-specific pneumonitis</td>
<td>1</td>
</tr>
<tr>
<td>Bronchopneumonia</td>
<td>1</td>
</tr>
<tr>
<td>Sarcoidsis</td>
<td>1</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1</td>
</tr>
</tbody>
</table>

*See Table 4 for abbreviations not used in the text.

TBBx in Febrile Neutropenic patients adds little value for infectious workup: Mayo Clin Proceedings

- Retrospective chart review of febrile neutropenic patients with pulmonary infiltrates.

Inclusion criteria:
- Neutropenic: ANC <0.5 x 10^9/L or <1 x 10^9/L with an expected nadir of <0.5 x 10^9/L
- Fever: isolated increase of body temperature to 38.3°C or a sustained temperature elevation to 38.0°C for at least 1 hour
- New pulmonary radiographic abnormality
- First occurrence of febrile neutropenia during 2002 and first bronchoalveolar lavage during this episode (n=36)

2005 Study in Mayo Clin Proceedings

- Diagnostic yield:

![Diagnostic yield chart](image)


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2005 Study in Mayo Clin Proceedings

In nonneutropenic patients, flexible bronchoscopy is considered a safe intervention, with a procedure-related mortality rate of 0.04% and a complication rate of 0.12%.\(^2\) If transbronchial biopsies are performed, the mortality rate increases to 0.12% and complications occur in 2% to 10% of patients.\(^2\) This increased risk is mainly attributed to higher rates of hemorrhage and pneumothorax. In the presence of thrombocytopenia, the risk of bleeding increases further (12%), and fatal outcomes due to massive hemorrhage after transbronchial biopsy have been reported.\(^2\)

**CONCLUSION:** The favorable safety record, good diagnostic yield, and frequent therapeutic implications support the routine use of BAL for the evaluation of pulmonary infiltrates in neutropenic patients. Bronchoalveolar lavage should be combined with the analysis of several sputum specimens. Transbronchial biopsy did only change the management of 1 patient.

Fungal organisms and non-infectious etiologies are often where we have seen the added value of TBBx over BAL

- To what extent does the BAL galactomannan assay change the landscape and improve the diagnostic yield for BALs?

- BAL galactomannan assays are less affected by antifungal treatment and neutrophil count than blood samples

- Galactomannan sensitivity has been reported as:
  - 19-38% in blood samples vs. 43-92% in BAL samples

<table>
<thead>
<tr>
<th>Studies</th>
<th>No. Studies</th>
<th>Pooled SEN (95% CE)</th>
<th>Pooled SPE (95% CE)</th>
<th>Pooled PLR (95% CE)</th>
<th>Pooled NLR (95% CE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall analysis</td>
<td>12</td>
<td>0.90 (0.79-0.96)</td>
<td>0.94 (0.90-0.98)</td>
<td>14.87 (8.89-24.90)</td>
<td>0.10 (0.04-0.24)</td>
</tr>
<tr>
<td>Cutoff of 0.5 for positivity</td>
<td>8</td>
<td>0.90 (0.79-0.94)</td>
<td>0.90 (0.85-0.92)</td>
<td>7.69 (5.75-10.28)</td>
<td>0.15 (0.07-0.25)</td>
</tr>
<tr>
<td>Cutoff of 1.0 for positivity</td>
<td>11</td>
<td>0.95 (0.72-0.93)</td>
<td>0.94 (0.80-0.97)</td>
<td>14.29 (8.13-24.50)</td>
<td>0.16 (0.08-0.31)</td>
</tr>
<tr>
<td>Cutoff of 1.5 for positivity</td>
<td>9</td>
<td>0.79 (0.46-0.85)</td>
<td>0.96 (0.93-0.98)</td>
<td>14.07 (10.05-22.92)</td>
<td>0.31 (0.17-0.57)</td>
</tr>
<tr>
<td>Cutoff of 2.0 for positivity</td>
<td>5</td>
<td>0.61 (0.39-0.90)</td>
<td>0.96 (0.92-0.98)</td>
<td>10.13 (8.07-12.25)</td>
<td>0.40 (0.23-0.70)</td>
</tr>
</tbody>
</table>

NLR = negative likelihood ratio; PLR = positive likelihood ratio; SEN = sensitivity; SPE = specificity. See Table 1 for expansion of other abbreviation.

References courtesy of Dr. Donowitz

Buchheidt et al. Curr Opin Infect Dis 2017
Park SY. CID 2011
Guo et al. Chest 2010
The data conflicts and is often based on retrospective review of procedures

What is the “standard” approach to these consults?

• Informal survey performed of our pulmonary faculty/fellows as well as select institutions in the US. n=12

• 91% recommend empiric antimicrobial therapy and/or bronch with BAL as first line intervention once we are consulted. Earlier BAL is preferred if possible.

• 9% would consider trans-bronchial biopsy during initial bronch depending on clinical factors.

• CT guided biopsy preferred if tissue required after initial a) negative bronch with BAL or b) lack of improvement despite empiric coverage

Are there guidelines?
Are there guidelines?

- German Society of Hematology and Medical Oncology (DGHO)

![Diagram](image)

*Annals of Oncology 26: 21–33, 2015*

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Are there guidelines?

- German Society of Hematology and Medical Oncology (DGHO)

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchoscopy and bronchoalveolar lavage (BAL) should be carried out using a standardized protocol.</td>
<td>A-II</td>
</tr>
<tr>
<td>Transbronchial biopsies are not recommended in feline immunodeficiency virus (FIV) and feline leukemia virus (FeLV) patients.</td>
<td>D-II</td>
</tr>
<tr>
<td>If a tissue sample for histological, microbiological and molecular workup is required, CT-guided side-cut percutaneous biopsy, video-assisted thoracoscopy or open lung biopsy should be used.</td>
<td>B-II</td>
</tr>
<tr>
<td>Microbiological workup of BAL samples should follow a standardized protocol.</td>
<td>B-II</td>
</tr>
<tr>
<td>Bronchoscopy and BAL should be available within 24 h after clinical indication has been established.</td>
<td>B-III</td>
</tr>
<tr>
<td>Urgent need to start or modify antifungal therapy should not be postponed by bronchoscopy and BAL.</td>
<td>A-III</td>
</tr>
<tr>
<td>Bronchoscopy and BAL should only be carried out in patients without critical hypoxia.</td>
<td>B-II</td>
</tr>
</tbody>
</table>

*Annals of Oncology 26: 21–33, 2015*
CT guided biopsy as a TBBx alternative

- 24 CT-guided perc needle aspirations in 21 immunocompromised patients
- 79% diagnostic yield
- No major complications

**TABLE 1** Underlying Conditions of 21 Immunocompromised Patients

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. of Aspirations</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal transplantation</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Hematologic malignancy</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Steroid therapy</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Chronic alcoholism</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>21</td>
</tr>
</tbody>
</table>

**TABLE 2** Pathologic Organisms Found in 19 Aspirates

<table>
<thead>
<tr>
<th>Organism</th>
<th>No. of Aspirations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria</td>
<td>3</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>4</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>1</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>1</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>2</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>1</td>
</tr>
<tr>
<td>Fungi</td>
<td>1</td>
</tr>
<tr>
<td>Aspergillus fumigatus</td>
<td>7</td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
<td>1</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>1</td>
</tr>
<tr>
<td>Nonspecific findings</td>
<td>5</td>
</tr>
</tbody>
</table>

Note: Two organisms were identified in one aspirate with positive findings.

AJR:175, July 2000
CT guided biopsy as a TBBx alternative

Do we have a recommended pathway here at UVA?
The Compromised Host with Pulmonary infiltrates: A Plan

24-48 hours from onset

Bronchoscopy with BAL (platelets of > 20,000)

24-48 hrs

Positive result?
meaningful? adjust Rx

Negative result
no clinical Δ

Obtain tissue

The compromised Host with Pulmonary Infiltrates: Plan cont’d

Obtaining Tissue

High Yield Lesions?
Platelets > 50-80k

TBBx

High yield lesion(s)
Platelets > 50-80k

CT-guided

? Fungal Infection

Dx unclear
platelets > 50-80K

Open/VATS

? Fungal Infection
Questions and Open Discussion