Investigation of Pneumonia in Deployed Troops

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Operation Iraqi Freedom, 2003

- U.S. Forces
- 19 cases of severe respiratory disease
  - 2 deaths
- EPICON launched
  - Active case finding
  - Questionnaire to determine risk factors
Severe Acute Pneumonia

Epidemiological Consultation (EPICON)

• Landstuhl, Germany
  - Late March 2003: 2 patients in ICU
  - 17 June 2003: First pneumonia death, reports of additional ICU patients
  - 12 July 2003: Second pneumonia death

• 17 July 2003: Army Surgeon General Tasking
  - Confirm severe pneumonia outbreak
  - 3 teams deployed
    • Iraq
    • Germany (Landstuhl)
    • United States

Method

• Questionnaire, database development
• Case finding
• Clinician interviews
• Review of charts, radiographs, laboratory tests
• Case interviews (surrogate for the two deaths)
• Autopsy review
• Follow-up clinical evaluations for 13 severe patients at WRAMC
  - Labs, PFTs, PPD, CXR, pulmonary / allergy evaluations
  - Revised questionnaire
• Tobacco analysis
Findings

CASE FINDING:
Acute Respiratory Failure / ARDS
(ICD-9-CM: 518.81, 518.82)

<table>
<thead>
<tr>
<th>Month</th>
<th># Cases</th>
<th>Non-Fatal</th>
<th>Fatal</th>
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Month 2003

Month 2004
**Demographics**

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<th>Age</th>
<th>Yrs</th>
<th>Rank</th>
<th>N (%)</th>
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<td>Median Range</td>
<td></td>
<td>≤ E4</td>
<td>24 (86)</td>
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<td></td>
<td>22</td>
<td>E5 - E9</td>
<td>3 (11)</td>
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<td></td>
<td>19-47</td>
<td>Officer</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td>Male</td>
<td>26 (93)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female</td>
<td>2 (7)</td>
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<tr>
<td>Race</td>
<td></td>
<td>White</td>
<td>27 (96)</td>
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<tr>
<td></td>
<td></td>
<td>Afr-Am</td>
<td>1 (4)</td>
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</table>

**Service**

- Army       22 (78)
- Navy       1 (4)
- Marine Corps 5 (18)

**Component**

- Active 15 (54)
- Reserves 6 (21)
- National Guard 7 (25)
Military Occupation

- Infantry: 3
- Armor: 2
- Artillery: 2
- Engineer: 3
- Mechanic: 1
- Truck driver: 2
- Fuel/Supply: 1
- Communications: 3
- Medical: 2

Severe Pneumonia: Time from Arrival in Theater to Onset

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th># Cases</th>
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<tbody>
<tr>
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<td>27</td>
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<td>30</td>
<td>0</td>
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</tbody>
</table>

Distribution of Symptoms (n=16)

- fevers or chills: 15
- shortness of breath: 12
- fatigue: 11
- cough: 10
- muscle or joint pain: 9
- chest pain: 7
- abdominal pain: 6
- vomiting: 4
- diarrhea: 4
- confusion: 4
- sore throat: 3
- sputum: 3
- nasal congestion: 2
- syncope: 1
- hemoptysis: 0
- rash: 0
Overview of Clinical Course (n=16)

- Symptoms & signs
  - Fever, respiratory distress
  - CXR w/ bilateral infiltrates (10 with pleural effusions)
- Antibiotics
  - Levofloxacin 88%
  - Ceftriaxone 65%
  - Doxycycline 59%
  - Imipenem 59%
  - Macrolide 47%
  - Vancomycin 24%
- Steroids given to 8 patients

Medical History

- Generally unremarkable
- No asthma
- Prescription medications
  - Simvastatin (1)
  - Malaria prophylaxis: medication and compliance varied
  - One with latent TB infection; non-compliant with INH
- Over-the-counter medications and supplements
  - Ibuprofen or aspirin as needed (3)
  - Vitamins (3)
  - Creatine (1)
  - OTC stimulant to stay awake (1)

Lab Findings

- Elevated WBC count (Median 13, range 7.3 - 37)
  - 10 patients with elevated eosinophil fraction
- Culture
  - Streptococcus pneumoniae (1) – sputum
  - Acinetobacter baumanii (1) – BAL fluid
- Urine antigen
  - Streptococcus pneumoniae (1)
- Serology
  - Coxiella burnetii (3)
  - Legionella spp. (1)
  - Low titers to various respiratory pathogens
  - Fungal & parasitic antibodies negative
- Immunology
  - Serum immunoprecipitation to tobacco leaf extracts negative
  - Most patients evidenced atopy by skin testing
Risk Factors Query

- No common exposures prior to illness
  - Occupational risk factors (daily duties, chemicals, munitions, fuel, etc)
  - Environmental risk factors (water, food, habitat, pollutants, etc)
  - Infectious risk factors (contact with locals, insects, animals, etc)
- Medications
- Smoking history
  - 16 smokers
    - 7 smoked both foreign and US tobacco
    - 9 began smoking during this deployment

Time Elapsed from Last Anthrax Immunization to Illness

Time Elapsed from Last Smallpox* Immunization to Illness

*One patient did not receive smallpox vaccine
Summary of Findings

- Higher rate of severe pneumonia compared to Army basic training posts
- No clear epidemiologic link
  - No relation in person, place or time
  - No common exposures identified
- Variety of possible infectious etiologies
- 10 cases with elevated eosinophils
  - New-onset smoking a possible risk factor
  - No common infectious cause, including parasites
  - No specific medication(s) unique to eos. patients
- No evidence of tobacco contamination

Pneumonia with Elevated Eosinophils

<table>
<thead>
<tr>
<th>Tissue involvement</th>
<th>Elevated Eosinophils</th>
<th>Yes</th>
<th>No</th>
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<tbody>
<tr>
<td>Lung + blood</td>
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<tr>
<td>Blood only</td>
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<td></td>
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<tr>
<td>Smoking</td>
<td></td>
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<tr>
<td>New-onset smoker</td>
<td>9</td>
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<tr>
<td>Chronic smoker</td>
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<td>6</td>
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<tr>
<td>Total</td>
<td>10</td>
<td>2</td>
<td>8</td>
</tr>
</tbody>
</table>

*Bronchoalveolar lavage fluid (3)
  Pleural fluid (1)
  Tissue from autopsy (1)

Elevated Eosinophils†
- Blood absolute count >600 cells/µl; pleural fluid and BAL fluid >5%

Time from illness onset to elevated eosinophils
- Mean = 7.5 days, median = 6.5 days, range 4-14 days

Acute Eosinophilic Pneumonia (AEP)
AEP Case Definition

- Febrile prodrome
- Acute onset of respiratory symptoms
- Chest film w/ infiltrates
- Definite case: Either lung biopsy with eosinophilic infiltration or BAL with >2% eos.
- Probable case: Never underwent BAL or lung biopsy but developed unexplained peripheral eosinophilia (total count > 250/mL AND eosinophils > 10% of differential)

AEP Epidemic Curve (first 27 months)

AEP Epidemic Curve (past 27 months)
Acute Eosinophilic Pneumonia (AEP)

- Etiology undetermined
- Evidence suggests one or more inhalational exposures in a predisposed individual
- Not an infection, but may present in conjunction with, or as a result of, infectious agents
- Initiation of tobacco smoking, or a significant increase in the quantity of tobacco smoked, appears to be a major risk factor

AEP Treatment

- Cessation of tobacco smoking
- Empiric treatment of CAP
  - 3rd generation cephalosporin (ceftriaxone, cefotaxime)
  AND
  - Respiratory tract quinolone (levofloxacin 500-750 mg IV qd or azithromycin 500 mg IV qd)
  AND
  - Doxycycline (100 mg IV bid)
- Corticosteroids
  - Solumedrol 80 mg IV q 8 hrs (or equivalent)
  - Begin taper over 2-4 weeks as symptoms resolve
- Pressure-control ventilation
- Evacuation from theater
Acute Eosinophilic Pneumonia Among US Military Personnel Deployed in or Near Iraq

Abstract
Acute eosinophilic pneumonia (AEP) is a rare disease of unknown etiology characterized by prominent features of fever, cough, dyspnea, and an elevated serum level of eosinophils. The disease usually remits with supportive therapy, but it may recur and be life-threatening. The etiology of AEP remains uncertain, although exposure to insecticides, environmental allergens, and medications is thought to be involved.

Objective
To determine the cause of AEP, to evaluate the risk factors for AEP, and to assess the outcome of an epidemiologic investigation.

Design, Setting, and Participants
A case-control study was conducted among 403 US military personnel deployed to Iraq during March 2003, comparing 45 cases of eosinophilic pneumonia to 358 controls. Separate case-control sets were recruited for those deployed to Iraq and Kuwait.

Results
There were 55 cases of AEP, including 15 cases of eosinophilic pneumonia identified in Kuwait, yielding an attack rate of 2 cases per 1000 person-weeks. The majority of cases had eosinophilic pneumonia identified during March 2003, and none were reported during the deployment to Kuwait. The proportion of cases meeting the diagnostic criteria for eosinophilic pneumonia did not vary by length of deployment or by region of deployment.

Conclusion
The results of this study suggest that the incidence of AEP is not increased among US military personnel deployed to Iraq. Further investigation is needed to determine the cause of AEP and to evaluate the risk factors associated with the disease.

Questions?