Identifying Meningitis During an Anthrax Mass Casualty Incident: Systematic Review of Systemic Anthrax Since 1880

Katherine Hendricks, MD, MPH
Medical Officer, Bacterial Special Pathogens Branch

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Overview

• Background
• What We Did & Why We Did It
• Methods
• Results
  – descriptive epidemiology
  – screening tools & their “test” characteristics
• Conclusions
Co-Author affiliations:

- Centers for Disease Control and Prevention, Atlanta, Georgia, USA
- Stanford University
- Cornell University, New York Presbyterian Hospital
- National Center for Emerging and Zoonotic Infectious Diseases
- Division of High Consequence Pathogens and Pathology/Bacterial Special Pathogens Branch
Notes

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Background

- Causative agent
- Anthrax epizootiology
- Types of anthrax with an emphasis on their fatality rates
  - diagnosis & treatment of anthrax meningitis
- Anthrax epidemiology
- Biowarfare
- Bioterrorism
Bacillus anthracis

• Causative agent of anthrax
  – nonmotile Gram positive rod

• Vegetative form produces two major toxins
  – lethal toxin
  – edema toxin

• Spores are the infective form
Anthrax Epizootiology

- Primarily disease of herbivores that ingest spores
- In this table susceptibility decreases as you read from left to right

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Types of Anthrax in Humans

- Cutaneous
- Gastrointestinal$^1$
- Inhalation$^2,3$
- Injection$^4$
- Meningitis$^5,6$

1. Beatty ME. 2003
2. Holty JE. 2006
4. Booth M. 2010
5. Sejvar JJ. 2005
Background: Cutaneous Anthrax

- Most common form
- Symptoms
  - itching → painless papule → vesicle → eschar
- Case fatality rate with antimicrobial treatment: <2%¹
## Mortality Rate for Untreated Cutaneous Anthrax

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<th>Cases</th>
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Hendricks KA . 2014.
Gastrointestinal Anthrax

• 2nd most common form of naturally occurring anthrax
• Incubation – usually 1 – 7 days
• Symptoms -- depend whether the infection has taken hold in the upper or lower portion part of the gastrointestinal system
• Case fatality rate with treatment: 40%¹

1. Beatty ME. 2003
Inhalation Anthrax

- Rare
- Incubation
  - in humans 1-43 days
  - in nonhuman primates 1-58 days

Holty JE. 2006
Inhalation Anthrax

• Symptoms
  – general: fever, chills, fatigue
  – localizing: cough, shortness of breath, or chest pain
  – involve other organ systems
    o gastrointestinal
    o central nervous system

• Case fatality rate with treatment
  – 1900-2000: 92%
  – 2001 and after: 47%

Holty JE. 2006
Chest X-Rays:
Normal and Patient with Inhalation Anthrax

Clear lungs and normal width mediastium

Mediastinal widening
Anthrax Meningitis

• Rare

• Complicates 41% - 55% of inhalation anthrax\(^1,2\)

• Can complicate
  - cutaneous anthrax
  - injection anthrax
  - gastrointestinal anthrax

1. Holty, 2006
2. Abramova. 1993
Anthrax Meningitis

- Can occur as a primary manifestation of anthrax (i.e., no other route of transmission)
- Case fatality rate for meningitis secondary to inhalation anthrax, 1900 – 2005: 100% (30/30) with meningitis died vs 81% (42/52) without meningitis

Holty, 2006
Brain, Normal Human vs. African Green Monkey with Anthrax Meningitis

Photo of African Green with inhalation anthrax, 2007, Dr. Nancy Twenhafel
Normal Procedure for Diagnosing Meningitis: Spinal Tap with Gram Stain & Cerebrospinal Fluid Culture
Intravenous Treatment for Systemic Anthrax When Meningitis Has Been Excluded

Bactericidal Agent

Protein Synthesis Inhibitor

1.

2.

PLUS

1. ciprofloxacin
   OR
   Alternatives for penicillin-susceptible strains
   PLUS
   clindamycin
   OR
   levofloxacin
   penicillin G
   linezolid

OR

moxifloxacin
ampicillin
doxycline
OR

meropenem
rifampin
OR

imipenem
OR

doripenem
OR

vancomycin
### Intravenous Treatment for Systemic Anthrax With Possible/Confirmed Meningitis

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<th>Bactericidal Agent (β-lactam)</th>
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Alternatives for penicillin-susceptible strains:
- Ciprofloxacin
- Meropenem
- Linezolid
- Levofloxacin
- Imipenem
- Clindamycin
- Moxifloxacin
- Doripenem
- Rifampin

1. Penicillin-susceptible strains
2. Penicillin G chloramphenicol
3. Ampicillin
Anthrax Epidemiology

- Butchering and eating of contaminated carcasses
  - both cutaneous and gastrointestinal cases
- Human contact with infected animals/animal products
  - “woolsorters disease”
- Incidental inhalation of spores from work or hobby
  - drummer cases
- Inhalation of spores from biowarfare or bioterrorism
  - accessible, can be mass produced, released as an aerosol, & has a high mortality rate
Definitions (see handout)

• **Mass Casualty Incident:** any incident in which emergency medical service resources, such as personnel and equipment, are overwhelmed by the number and severity of casualties\(^1\)

• **Biowarfare:** the use of microorganisms (pathogens) or the products of living organisms (toxins) to kill or incapacitate humans, animals, or plants as an act of war (i.e., as a weapon)

• **Bioterrorism:** the use of microorganisms (pathogens) or the products of living organisms (toxins) to inflict harm on a ...[civilian] population, including animals and crops\(^2\)

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Post WWII Bioweapons Production

- **United States**
  - Research and development (R&D): 1949-69
    - *Bacillus anthracis* (anthrax)
    - *Franciscella tularensis* (tularemia)
    - *Brucella suis* (brucellosis)
  - Peak production 1951-62
  - Stockpiles destroyed in 1969 by executive order of President Nixon

Courtesy Dr. Nathaniel Hupert
Post WWII Bioweapons Production

- **USSR**
  - R&D 1945-92
  - 40-50 institutes
  - Weaponized and stockpiled
    - *Bacillus anthracis*
    - Smallpox
    - *Yersinia pestis* (plague)

- **Iraq**
  - Early 1980s
  - Weaponized & stockpiled:
    - *Bacillus anthracis*
    - Botulinum toxin
    - Aflatoxin

Courtesy Dr. Nathaniel Hupert
Biowarfare

- WWI, animals targeted
- WWII, cold war
- Sverdlosk (USSR) 1979, accidental release from BW facility with ≥ 96 cases and 66 deaths
• Bioterrorism
  - 1993 attack by Japanese religious group failed
  - 2001 attack in US via the mail produced 22 cases of anthrax; half were cutaneous, half were inhalation, and 5 of the 11 patients with inhalation anthrax died
Investigation of Bioterrorism-Related Anthrax, United States, 2001: Epidemiologic Findings

After terrorist attacks on the World Trade Center and the Pentagon in 2001, envelopes containing B. anthracis spores were mailed to news media companies and government officials, leading to the first bioterrorism-related cases of anthrax in the United States. We report the combined findings from epidemiologic and laboratory investigations of these cases conducted through coordinated efforts of medical and laboratory communities and local, state, and federal public health and law enforcement agencies.

Bioterrorism-Related Inhalational Anthrax: The First 10 Cases Reported in the United States

From October 4 to November 2, 2001, the first 10 confirmed cases of inhalational anthrax were identified in the United States. Epidemiologic and historical evidence supported the presence of Bacillus anthracis spores in powdered materials. Monitoring and surveillance were enhanced through health care provider and public health agency partnerships. In the early 1990s, human cases of inhalational anthrax in the United States were associated with exposure to spores in mail. After the terrorist attacks of 2001, human cases of inhalational anthrax were associated with exposure to anthrax spores in nonmedical powder.

Inhalational anthrax is a disease caused by inhalation of B. anthracis spores. The disease is characterized by a prodrome of fever, malaise, nausea, and vomiting, followed by the development of respiratory symptoms including cough, dyspnea, and chest pain. The disease is often fatal if untreated. The diagnosis of inhalational anthrax is typically made through the identification of B. anthracis spores in respiratory specimens. Treatment with antibiotics is critical for survival.

Inhalational anthrax can be prevented by avoiding exposure to B. anthracis spores. This includes avoiding contact with infected animals or their products, as well as avoiding exposure to powdered materials that may contain B. anthracis spores. Public health measures, such as improving mail handling practices and increasing the use of mail handling equipment, have been implemented to reduce the risk of exposure to B. anthracis spores during the 2001 attacks.

The investigation of the 2001 anthrax attacks highlighted the importance of public health preparedness and response. It emphasized the need for enhanced surveillance and response capabilities to detect and control future bioterrorism threats.

Note: The information provided is a summary of key points from the referenced articles and does not constitute medical advice.

References:


Additional Resources:

World Health Organization Estimate of Anthrax Mass Casualty Incident Morbidity & Mortality

50 kg *B. anthracis*

2 kilometer line upwind & 90° to wind direction

City of 5 Million

250,000 casualties including 100,000 fatalities

100,000 People
Animal (Stern) vaccination started in 1957 after OK epizootic. Recommended for annual use in animals in endemic regions.

2001 anthrax letter attacks
Anthrax, particularly anthrax meningitis is deadly.

It’s difficult (i.e., costly in terms of infrastructure and time) to diagnose in the traditional manner.

Patients with anthrax meningitis need 3 antimicrobials; patients with just systemic anthrax need 2 antimicrobials.

In a mass casualty incident, we could have thousands of patients who need diagnosis and treatment.

There are too few cases to answer questions prospectively.
WHAT WE DID AND WHY WE DID IT
Objectives

1) Improve the ability of clinicians to triage and monitor patients for meningitis during an anthrax mass casualty incident
   - Could we substitute a checklist for the gold standard?
2) Identify factors associated with meningitis outcomes
3) Inform public health policy regarding preparedness for and response to an anthrax mass casualty incident
Systematic Review of Systemic Anthrax Cases, 1880 - 2013

- Guiding Questions

1) What symptoms or signs might predict meningitis in patients with systemic anthrax?

2) How well do predictions based on symptoms and signs compare with predictions based on diagnostic test results (e.g., lumbar puncture results)?

3) What variables are associated with survival?
• Everything hinged on us finding cases in the published literature

• Denominator: we chose to use systemic anthrax rather than inhalation anthrax because
  – notable outbreaks include noninhalation cases
  – meningitis can complicate any type of anthrax
METHODS
Why Use a Librarian to Perform Your Search?

• To determine whether your proposed systematic review has already been done
• To help formulate your questions
• To clarify and refine your search strategy
• To determine which databases are appropriate

Why Use a Librarian to Perform Your Search (cont.)?

• To avoid problems with nomenclature
• To determine which databases can be accessed and the search syntax/truncation requirements for each
• To be able to identify germane grey literature

Why Use a Librarian to Perform Your Search (cont.)?

- To collect and file the “yes” articles from the search
- For help in writing the methodology section of the review
- To generate the final bibliography
- Because the interdisciplinary team needed to do a systematic review necessarily includes a librarian

Methods (see handout)

• Search string developed in collaboration with librarians at CDC and Weill Medical College

• Search string captured English-language publications
  – triage of patients in an anthrax mass casualty incident
  – diagnostic tests and test characteristics (e.g., sensitivity/specificity) related to anthrax meningitis

• Twelve databases searched: inception through October 2013

• Subject matter experts also identified articles

• Hand-search of references for review articles (i.e., snowballing)
Study Identification (see handout)

6054 articles identified through searching:
356  CAB
158  CINAHL
22   DTIC
28   EconLit
330  Embase
585  FEDRIP
1241 Global Health
  6   NTIS
3028 Medline
279  Web of Science
  1   WHO
  20  WorldCat

1056 additional articles identified through subject matter experts and manual searches of the references for review articles

7110 articles to screen
Study Screening

7110 articles to screen

1667 duplicates removed

5443 articles reviewed by title/abstract

4622 articles excluded because they lacked relevant information

821 articles for full-text review
821 articles for full-text review

515 articles were excluded because they lacked pertinent information

306 articles from which to extract case data

690 cases were extracted in duplicate

30 cases were duplicates

660 cases

363 case met criteria for systemic anthrax
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<td>34</td>
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<td>36</td>
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</tbody>
</table>
Case Definitions (see handout)

- Anthrax Case
- Systemic Illness
- Meningitis
- Fulminant / Prodromal
- UN Country Codes
- Completeness Score
Marissa Person, MSPH
Programming to Define Systemic Illness in Children

```javascript
if . < age < 18 then do;
    if 0 < _43 < 36 or _43 > 38.5 or _43 in ("<35","ANL","BNL","febrile") then SIRS1=1; *Temp on admittance;

    if 13 le _14*1 lt 18 then do:
        if _46*1 > 110 or substr(_46,1,5)="tachy" or upcase(_48)="Y" or upcase(_48)="ANL" then SIRS2=1;
        if _51*1 > 14 then SIRS3=1;
        if _122a > 11 or _122a="leukocytosis" or _122a="ANL" or 0 < _122a < 4.5 then SIRS4=1; *added ANL to all age groups per Kate on 2/26/2016;
    end;
    if 6 le _14*1 lt 13 then do:
        if _46*1 > 130 or substr(_46,1,5)="tachy" or upcase(_48)="Y" or upcase(_48)="ANL" then SIRS2=1;
        if _51*1 > 18 then SIRS3=1;
        if _122a > 15.5 or _122a="leukocytosis" or _122a="ANL" or 0 < _122a < 4.5 then SIRS4=1;
    end;
    if 2 le _14*1 lt 6 then do:
        if _46*1 > 140 or substr(_46,1,5)="tachy" or upcase(_48)="Y" or upcase(_48)="ANL" then SIRS2=1;
        if _51*1 > 22 then SIRS3=1;
        if _122a > 15.5 or _122a="leukocytosis" or _122a="ANL" or 0 < _122a < 8 then SIRS4=1;
    end;
    if 1/12 le _14*1 lt 2 then do:
        if _46*1 > 180 or substr(_46,1,5)="tachy" or upcase(_48)="Y" or upcase(_48)="ANL" then SIRS2=1;
        if _46*1 < 90 then SIRS2=1;
        if _51*1 > 34 then SIRS3=1;
        if _122a > 17.5 or _122a="leukocytosis" or _122a="ANL" or 0 < _122a < 5 then SIRS4=1;
    end;
    if 1/52 le _14*1 lt 1/12 then do:
        if _46*1 > 100 or substr(_46,1,5)="tachy" or upcase(_48)="Y" or upcase(_48)="ANL" then SIRS2=1;
        if _46*1 < 100 then SIRS2=1;
        if _51*1 > 40 then SIRS3=1;
        if _122a > 19.5 or _122a="leukocytosis" or _122a="ANL" or 0 < _122a < 5 then SIRS4=1;
    end;
    if 0 le _14*1 lt 1/52 then do:
        if _46*1 > 180 or substr(_46,1,5)="tachy" or upcase(_48)="Y" or upcase(_48)="ANL" then SIRS2=1;
        if _46*1 < 100 then SIRS2=1;
        if _51*1 > 50 then SIRS3=1;
        if _122a > 34 or _122a="leukocytosis" or _122a="ANL" then SIRS4=1;
    end;
    if SIRS1=1 or SIRS2=1 or SIRS3=1 or SIRS4=1 then systemic=1;
```
Case Definitions

• **Completeness Score**$^{1,2}$ **Items:**
  - author, title, demographic information
  - chief complaint
  - symptoms, signs, laboratory results on presentation
  - key laboratory results over the course of illness
  - whether and when key complications occurred
  - treatments
  - outcomes including autopsy findings
  - timing for symptoms, signs, tests, treatments, and outcomes

1. Case REport (CARE) checklist
2. toxicology case report checklist of Lavergne et al
Data Synthesis & Analysis

- Descriptive statistics regarding
  - demographic patient characteristics
  - route of transmission
  - symptoms & signs *at presentation*
  - laboratory results *on presentation*
  - presence of meningitis
  - treatment
  - completeness score
Data Synthesis & Analysis

- Stratified by age
- Geographic and temporal trends
- Divided our adults into two cohorts using random sampling
  - 80%: the derivation cohort
  - 20%: the validation cohort
- Retained the full pediatric cohort for a validation cohort
Data Synthesis & Analysis

- Used the 80% sample to determine independent predictors of anthrax meningitis
  - tested differing combinations of predictors and thresholds for a potential anthrax meningitis screening tool (i.e., a
  - variables chosen based on
    - univariate statistical significance
    - historic precedent
    - historic importance for meningitis
    - potential availability and utility
Data Synthesis & Analysis

• Compared checklists with various signs/symptoms to identify the one with best test characteristics

• Best checklists were then tested (i.e., validated) in the adult and pediatric cohorts

• Finally we assessed whether reporting bias affected our results. To do this, determined whether the results varied if we used cases with completeness scores in the top 50%
RESULTS : GENERAL
Descriptive Epidemiology

- 363 patients were identified with systemic anthrax
- 307 (85%) adults, 56 (15%) children
- Hospitalized, 93%
- 132 (36%) had meningitis
  - 89% confirmed
  - 5% probable
  - 6% suspected
Descriptive Epidemiology

- Mortality rate, 63%
  - adults with meningitis 95%
  - children with meningitis 79%
  - adults without meningitis 50%
  - children without meningitis 25%
Descriptive Epidemiology

- **Routes of transmission**
  - Cutaneous – 52%
  - Inhalation – 23%
  - Ingestion – 13%
  - Injection – 2%
  - None apparent – 9%
Descriptive Epidemiology

• Completeness score
  – Range, 5-15
  – Median, 11
  – 95% scored 8 or higher
Temporal Trends in Patients Reported with Systemic Anthrax by Meningitis Status & Completeness, 1880-2013

Published Cases

Non-Meningitis
Meningitis
Completeness Score

Time Increments

1880 - 1899
1900 - 1919
1920 - 1939
1940 - 1959
1960 - 1979
1980-1999
2000+

Completeness
GUY'S HOSPITAL.
A FATAL CASE OF ANTHRAX INVOLVING THE BRAIN.
(Under the care of Mr. R. Clement Lucas.)
[For the particulars of this case we are indebted to Mr. A. T.
Rake, House-Surgeon.]
M. S., aged 48, a waterside labourer, was admitted on December 16th, 1892, suffering from a sore on his neck. In the course of his work he was often brought in contact with hides; he remembered having laid his hands on two bales of hides, on board a vessel in the river, on December 13th. On December 14th he noticed a small pimple on the side of his neck. This did not itch at all, and caused him no inconvenience. The pimple increased in size, became more inflamed, and a head formed. The "head" burst on the morning of admission, and a little yellow discharge came away from it. His neck was rather stiff, but he had had no headache, and had not felt unwell. One of his mates, having seen the sore, advised him to come up to the hospital at once, as the danger of infection from hides is well known in the neighbourhood.
The patient's condition did not change, and respiration ceased at 8.45 A.M. The temperature was 106° as he was dying.

Post-mortem Examination.—The pia mater was intensely congested throughout its whole extent, including the velum interpositum. There were numerous hæmorrhages beneath the arachnoid, the largest (the size of a crown piece) over the right middle lobe. There was also a hæmorrhage into the posterior part of the left lenticular nucleus. Dr. Washbourn found numerous bacilli in the blood extravasated beneath the arachnoid, but none in some blood taken from one of the saphenous veins. The lungs were much engorged, but there were no hæmorrhages into them, nor were there any intestinal lesions. The spinal cord was not examined.
Geographic Trends in Patients Reported with Systemic Anthrax, 1880-2013

1880 – 1959, n=189

- N America
- Europe
- Asia
- Africa
- Other

1960 – 2013, n=173

- N America
- Europe
- Asia
- Africa
- Other
RESULTS : SPECIFIC
Guiding Questions # 1

What symptoms or signs might predict meningitis in patients with systemic anthrax?
# Odds Ratios (ORs) and Significance Testing (see Handout)

<table>
<thead>
<tr>
<th>Event happens (i.e., Survival)</th>
<th>Standard Treatment</th>
<th>New Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event doesn’t happen (i.e., Death)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Odds Ratio (OR)** = \( \frac{A \times D}{B \times C} \)

**p-value** – probability of your result if nothing is going on (i.e., the null hypothesis); \( P = 0.05 \) is often used as the cut-off for statistical significance.
Test Characteristics for Screening Tools (see Handout)

• **Sensitivity**: the proportion of actual positives which are correctly identified as such

• **Specificity**: the proportion of negatives which are correctly identified as such

• **Positive Likelihood Ratio (LR+)**: the probability of a person who has the disease testing positive divided by the probability of a person who does not have the disease testing positive

• **Negative Likelihood Ratio (LR-)**: the probability of a person who has the disease testing negative divided by the probability of a person who does not have the disease testing negative
### Clinical Presentation, Adults

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Meningitis N = 113</th>
<th>No Meningitis N = 194</th>
<th>OR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever/chills</td>
<td>77%</td>
<td>55%</td>
<td>2.8 (1.6 – 4.9)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>44%</td>
<td>19%</td>
<td>3.3 (2.0 – 5.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Headache</td>
<td>43%</td>
<td>20%</td>
<td>3.1 (1.8 – 5.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Severe headache</td>
<td>20%</td>
<td>4%</td>
<td>5.6 (2.3 – 16.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>79%</td>
<td>13%</td>
<td>25 (13 – 49)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td>38%</td>
<td>2%</td>
<td>39 (12 – 200)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Meningeal signs</td>
<td>40%</td>
<td>0%</td>
<td>178 (39 – ∞)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Other neuro deficits</td>
<td>44%</td>
<td>0%</td>
<td>216 (48 – ∞)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
## Variables of Interest for the Checklist, Adults

<table>
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<th>Characteristic</th>
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<td><strong>216 (48- ∞)</strong></td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
## Potential Screening Tools (i.e., Checklists) for Meningitis in an Anthrax Mass Casualty Incident

<table>
<thead>
<tr>
<th>Symptom/Sign</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>LR+</th>
<th>LR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 of the following: AMS, MS, ON</td>
<td>.80</td>
<td>.88</td>
<td>6.4</td>
<td>.22</td>
</tr>
<tr>
<td>2 of the following: AMS, MS, ON</td>
<td>.60</td>
<td>1.0</td>
<td>182</td>
<td>.40</td>
</tr>
<tr>
<td>1 of the following: SHA, AMS, MS, ON</td>
<td>.87</td>
<td>.84</td>
<td>5.3</td>
<td>.15</td>
</tr>
<tr>
<td>2 of the following: SHA, AMS, MS, ON</td>
<td>.66</td>
<td>.99</td>
<td>100</td>
<td>.35</td>
</tr>
<tr>
<td>1 of the following: SHA, AMS, MS, ON, N / V</td>
<td>89</td>
<td>.67</td>
<td>3</td>
<td>.17</td>
</tr>
<tr>
<td>2 of the following: SHA, AMS, MS, ON, N / V</td>
<td>.75</td>
<td>.95</td>
<td>16</td>
<td>.27</td>
</tr>
</tbody>
</table>

SHA = severe headache, AMS = altered mental status, MS = meningeal signs, ON = other neurological signs, N / V = nausea / vomiting
Guiding Questions # 2

How well do predictions based on symptoms and signs compare with predictions based on diagnostic test results (e.g., lumbar puncture results)?
### Validity of Screening Tools (i.e., Checklists) in the Adult Validation Sample & Pediatric Group & Sensitivity Analysis

<table>
<thead>
<tr>
<th>Screening Tool &amp; Test Sample</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 of the following: SHA, AMS, MS, ON</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Adults (N = 61)</td>
<td>.89</td>
<td>.86</td>
</tr>
<tr>
<td>• Children (N = 55)</td>
<td>.83</td>
<td>.89</td>
</tr>
<tr>
<td>2 of the following: SHA, AMS, MS, ON</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Adults (N = 61)</td>
<td>.63</td>
<td>.98</td>
</tr>
<tr>
<td>• Children (N = 55)</td>
<td>.39</td>
<td>.99</td>
</tr>
</tbody>
</table>

SHA = severe headache, AMS = altered mental status, MS = meningeal signs, ON = other neurological signs
### Validity of Screening Tools (i.e., Checklists) in the Adult Validation Sample & Pediatric Group

<table>
<thead>
<tr>
<th>Screening Tool &amp; Test Sample</th>
<th>LR+</th>
<th>LR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 of the following: SHA, AMS, MS, ON</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults (N = 61)</td>
<td>6.3 (2.9–13.4)</td>
<td>0.12 (0.03–0.46)</td>
</tr>
<tr>
<td>Children (N = 55)</td>
<td>7.7 (3.0–19.9)</td>
<td>0.19 (0.07–0.53)</td>
</tr>
</tbody>
</table>

| 2 of the following: SHA, AMS, MS, ON |                   |                   |
| Adults (N = 61)             | 27 (4-189)        | 0.38 (0.21-0.68)  |
| Children (N = 55)           | 29 (2-486)        | 0.62 (0.43-0.90)  |

SHA = severe headache, AMS = altered mental status, MS = meningeal signs, ON = other neurological signs
Missed Cases

- A total of 16 cases were undetected in our three cohorts (adult 80% sample, adult 20% sample, and pediatric sample) by our tool that evaluated signs/symptoms at presentation
  - 16/132 (12%)

- 7/16 (44%) developed signs or symptoms later
Guiding Questions # 3

What variables are associated with survival?
### Prognostic Factors for Outcome on Univariate Analysis, All Meningitis Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Died N = 122</th>
<th>Lived N = 10</th>
<th>OR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/vomiting</td>
<td>43%</td>
<td>80%</td>
<td>0.2 (0.0 – 1.0 )</td>
<td>0.06</td>
</tr>
<tr>
<td>Headache</td>
<td>41%</td>
<td>80%</td>
<td>0.2 (0.0 – 0.9)</td>
<td>0.04</td>
</tr>
<tr>
<td>Severe headache</td>
<td>17%</td>
<td>50%</td>
<td>0.2 (0.0 – 1.0)</td>
<td>0.05</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>80%</td>
<td>40%</td>
<td>5.7 (1.3 – 29.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>CSF WBCs (cells/µl), mean</td>
<td>3,634</td>
<td>885</td>
<td>NA</td>
<td>0.02</td>
</tr>
<tr>
<td>WBCs (cells/µl), mean</td>
<td>21,000</td>
<td>10,900</td>
<td>NA</td>
<td>0.05</td>
</tr>
<tr>
<td>Multiple antimicrobials</td>
<td>25%</td>
<td>70%</td>
<td>0.1 (0.0 – 0.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>Bactericidal therapy</td>
<td>53%</td>
<td>100%</td>
<td>0.08 (0.0 – 0.4)</td>
<td>0.005</td>
</tr>
</tbody>
</table>
Limitations

• Publication bias
• Underestimation of disease
  – patients with quickly fatal conditions may not have been taken to hospital
• Only English language
• Pertinent negatives possibly omitted
• Although signs/symptoms didn’t change, treatment changed significantly
  – difficult to comment on newer modalities
CONCLUSIONS
Conclusions

• Confirmed the high prevalence of anthrax meningitis among patients with systemic anthrax, regardless of exposure route

• Confirmed lethality of systemic anthrax with meningitis compared to systemic anthrax without meningitis (92.4% vs 46.0%, p <0.001)
Conclusions

Confirmed Previously Published Information
Institute of Medicine Definitions

• **Conventional standard of care** is the usual standard of care in noncrisis settings.

• **Contingency standard of care** is equivalent care to conventional settings, except that the care might involve different methodologies, medications, and locations.

• **Crisis standard of care** is a situation in which resource limitations require medical care prioritization. In crisis settings, care might not be initiated and might conceivably be withdrawn from persons to allow resources to be allocated to persons with the highest likelihood of survival or benefit.
### Conclusions

<table>
<thead>
<tr>
<th>Standard of Care</th>
<th>Response to Screening Questions for Patients with Systemic Anthrax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional*</td>
<td>Lumbar Puncture</td>
</tr>
<tr>
<td>Contingency</td>
<td>2 Antimicrobials</td>
</tr>
<tr>
<td>Crisis</td>
<td>2 Antimicrobials</td>
</tr>
</tbody>
</table>

* Under a conventional standard of care, healthcare personnel would not use a checklist; instead they would perform a traditional history and physical
Conclusions

Answered Questions 1 & 2
Conclusions

• Survival was increased in patients who received bactericidal antimicrobials and in those who received multiple antimicrobials

• 7/16 that were missed by screening on admission later developed symptoms / signs
  – the tool should also be used for monitoring
Identifying Meningitis During an Anthrax Mass Casualty Incident: Systematic Review of Systemic Anthrax Since 1880

Stefan Katharios-Lanwermerayer,1 Jon-Erik Holty,2 Marissa Person,1 James Sejvar,1 Dana Haberling,1 Heather Tubbs,3 Dana Meaney-Delman,4 Satish K. Pillai,3 Nathaniel Hupert,5,a William A. Bower,1,a and Katherine Hendricks1,a

1Division of High-Consequence Pathogens and Pathology, Centers for Disease Control and Prevention, Atlanta, Georgia; 2Pulmonary, Critical Care and Sleep Medicine Section, VA Palo Alto Healthcare System Department of Medicine, Stanford University, California; 3Division of Preparedness and Emerging Infections, and 4National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; and 5Departments of Healthcare Policy and Research and of Medicine, Weill Medical College, Cornell University, New York

**Background.** *Bacillus anthracis*, the causative agent of anthrax, is a potential bioterrorism agent. Anthrax meningitis is a common manifestation of *B. anthracis* infection, has high mortality, and requires more aggressive treatment than anthrax without meningitis. Its rapid identification and treatment are essential for successful management of an anthrax mass casualty incident.

**Methods.** Three hundred six published reports from 1880 through 2013 met predefined inclusion criteria. We calculated descriptive statistics for abstracted cases and conducted multivariable regression on separate derivation and validation cohorts to identify clinical diagnostic and prognostic factors for anthrax meningitis.
Clinical Framework and Medical Countermeasure Use During an Anthrax Mass-Casualty Incident

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Dr. Peter Turnbull

Anthrax vaccines: past, present and future

Peter C.B. Turnbull

Most livestock vaccines in use throughout the world today for immunization against anthrax are derivatives of the live spore vaccine formulated by Sterne in 1893 and still in use for effective control in many countries with considerable reduction, sometimes complete elimination, of the disease in animals and, since man generally acquires the infection from livestock, in man as well. However, there are some contraindications of its use and situations in which it is contraindicated. The human anthrax vaccines (UK vaccine) need to be administered under strict conditions.
Experimental **anthrax** vaccines: efficacy of adjuvants combined with protective antigen against an aerosol *Bacillus anthracis* spore challenge in guinea pigs
B Ivins, P Fellows, L Pitt, J Estep, J Farchaus... - *Vaccine, 1995* - Elsevier

... Turnbull; **Anthrax** vaccines: past, present and future. *Vaccine, 9* (1991), pp. 533–539. ... Turnbull;

**Anthrax** vaccine development: a continuing story. A. Mizrahi (Ed.), *Bacterial Vaccines, Advances in Biotechnological Processes* (4th edn), vol. 13, , Alan R. Liss, New York (1990), pp. ...

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**Anthrax** vaccines: past, present and future
PCB Turnbull - *Vaccine, 1991* - Elsevier
Abstract Most livestock vaccines in use throughout the world today for immunization against anthrax are derivatives of the live spore vaccine formulated by Sterne in 1937 and still use descendants of his strain 34F 2. Credit belongs to this formulation for effective control in ...

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Development of antibodies to protective antigen and lethal factor components of **anthrax** toxin in humans and guinea pigs and their relevance to protective immunity.
PC Turnbull, MG Broster, JA Carman... - *Infection and ...*, 1986 - Am Soc Microbiol
ABSTRACT A competitive inhibition enzyme-linked immunosorbent assay (ELISA) was developed to detect antibodies in serum to the protective antigen (PA) and lethal factor (LF) components of anthrax toxin. Current human vaccination schedules with an acellular ...
While anthrax was once a scourge in many parts of the world, it has steadily declined in incidence. Nevertheless, anthrax has become increasingly interesting as its causative agent, Bacillus anthracis, has been recognized as one of the most important causative agents of disease in the field of industrial microbiology. In the past, industrial microbiologists had to be concerned with the mechanisms of infection and pathology caused by Bacillus anthracis. Today, with the advent of modern technology, we can better understand the biology of anthrax and its role in disease.

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Dr. Phillip S. Brachman
Questions?

Kate Hendricks, MD, MPH&TM, kah1@cdc.gov, 404.639.3153