BUGS
DRUGS
AND MEDICAL THUGS
A HISTORY OF SYPHILIS, THE INVENTION OF PENICILLIN, AND RESEARCH ON VULNERABLE POPULATIONS

Maggie Hopkins, MD, MBA
Clinical Chemistry April 2013
University of Utah CME Statement

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- Speakers are also expected to openly disclose intent to discuss any off-label, experimental, or investigational use of drugs, devices, or equipment in their presentations.
- This speaker has nothing to disclose.
Learning objectives

• After attending this seminar the attendee should be able to:

1. Describe the four stages of syphilis with defining characteristics of each stage.

2. List the compounds discovered and used historically in the treatment for syphilis in order of efficacy.

3. Critically evaluate the ethicality of research conducted on human subjects in Tuskegee and Guatemala.

4. Compare pros and cons of the traditional and reverse algorithms for syphilis screening.
Outline

- Case from UH
- Bugs
  - Description of syphilis
  - Symptoms and stages of disease
  - History of syphilis
- Drugs
  - Mercury
  - Salvarsan
  - Penicillin
- Medical Thugs
  - Tuskegee, Alabama
  - Guatemala
- Current diagnostic algorithms and tests for syphilis
- Conclusion
A CASE FROM UNIVERSITY HOSPITAL
New Orleans, LA
Case History

• 19-year-old AA female brought to the ED

• Paramedics report her mother found her unresponsive

• Six months ago, the patient had an episode of autoimmune hemolytic anemia
  • Treated with a blood transfusion
Physical Exam

<table>
<thead>
<tr>
<th>Vitals</th>
<th>result</th>
<th>normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td>101/72</td>
<td>90/60 to 120/80 mm/Hg</td>
</tr>
<tr>
<td>heart rate</td>
<td>123</td>
<td>60 - 100 beats per minute</td>
</tr>
<tr>
<td>respirations</td>
<td>32</td>
<td>12 - 18 breaths per minute</td>
</tr>
<tr>
<td>oral temperature</td>
<td>34.8°C</td>
<td>36.5 to 37.5 Celsius</td>
</tr>
<tr>
<td>pulse oximetry</td>
<td>100% on room air</td>
<td>94% to 99% SpO2</td>
</tr>
</tbody>
</table>

- Rash on palms and soles
## Labs

<table>
<thead>
<tr>
<th>Lab</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial blood gas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>6.92</td>
<td>7.35 – 7.45</td>
</tr>
<tr>
<td>CO2</td>
<td>9</td>
<td>35 – 45 mmHg</td>
</tr>
<tr>
<td>HCO3</td>
<td>2</td>
<td>22 – 26 mEq/L</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>1500</td>
<td>70 – 100 mg/dL</td>
</tr>
<tr>
<td>Urine ketones</td>
<td>++ positive</td>
<td>negative</td>
</tr>
</tbody>
</table>

**Acidosis**

**Respiratory alkalosis**

**Metabolic Acidosis**
Diagnosis?

- Diabetic Ketoacidosis

Treatment?

- IV fluid
- Insulin
Clinical Course

• Gave hydration and insulin therapy
• Patient regained consciousness
• Able to converse
  ➢ Stated she was feeling “a little better”

• Repeat morning physical exam:
  • Medical student noticed a peculiar rash on patients palms and soles of her feet…
Palmar Rash differential

• Hand, Foot and Mouth disease
• Psoriasis
• Rocky Mountain Spotted Fever
• Erythema Multiforme
• Secondary Syphilis
ID workup

• HIV: negative
• VDRL: positive
• Confirmatory test, FTA-ABS: positive
• Diagnosis:
  • Syphilis
BUGS

Treponema pallidum
Syphilis

- Caused by the bacterium *Treponema pallidum*
- Spirochete
- Motile
Transmission

- Sexual contact
- Mucous membranes
- Placental
- Blood products

- 30-60% exposed will be infected
Incidence

• 46,042 new US cases diagnosed in 2011
  • 1/3 of these primary or secondary
  • 360 cases of congenital syphilis

• CDC Est. 55,400 new infections annually

• At risk populations:
  • MSM, 72% of new cases
  • HIV
  • Babies of infected mothers

http://www.cdc.gov/std/syphilis/stdfact-syphilis.htm
Clinical progression

• If untreated, progresses through 4 stages:
  ✓ Primary
  ✓ Secondary
  ✓ Latent
  ✓ Tertiary

• Congenital syphilis
Primary Syphilis

• 2-4 weeks after initial infection
• Chancre

http://www.news-medical.net/health/What-is-Syphilis.aspx
Secondary Syphilis

- About 2 months after the initial sore disappears…
  - Constitutional symptoms
  - Weight loss, hair loss and a skin rash
Latent syphilis

- No obvious symptoms during this period
- Can continue indefinitely
- Fifty to seventy percent of patients do not progress
Tertiary syphilis

- 10+ years later…
- Lesions on the skin, bone, and vital organs
  - “gummas”
- Cardiovascular
- Neurosyphilis
“Cor bovinum”
Neurosyphilis

- Psychiatric complaints
  - “general paresis of the insane”
- Argyle Robinsons pupil
- Tabes Dorsalis
Tabes Dorsalis

CONGENITAL SYPHILIS

- Passed through the placenta
- Skeletal deformities
Syphilis

• Advanced stages can mimic nearly any disease...

• “the great imitator”
• “The physician who knows syphilis knows medicine.”
  - Sir William Osler

Syphilis inspired literature, art, poetry…
Syphilis limerick

There was a young man from Black Bay
Who thought syphilis just went away
He believed that a chancre
Was only a canker
That healed in a week and a day.

But now he has “acne vulgaris” –
(Or whatever they call it in Paris);
On his skin it has spread
From his feet to his head,
And his friends want to know where his hair is.

There’s more to his terrible plight;
His pupils won’t close in the light
His heart is cavorting,
His wife is aborting,
And he squints through his gun-barrel sight.

Arthralgia cuts into his slumber;
His aorta in need of a plumber;
But now he has tabes,
And saber-shinned babies,
While of gummas he has quite a number.

He’s been treated in every known way,
But his spirochetes grow day by day;
He’s developed paresis,
Has long talks with Jesus,
And he thinks he’s the Queen of the May

Anonymous, Ca 1920
HISTORY OF SYPHILIS
Syphilis

- Syphilis first ‘appeared’ in Europe in 1496
- Caused terrible sickness
  - severe ulceration of the genitals
  - pustules on the face and body
  - foul smell
  - soft tissue eaten away to the bone
Origins

- 2 theories:
  1. Christopher Columbus
  2. Already in Europe

- 1494 - King Charles VIII of France attacked Naples
- By end of 15th century - severe syphilis pandemic
- Physicians announced a new disease
New disease gets a name

• "the Spanish disease," "French pox," or the "Neapolitan evil"
• "Great Pox," in distinction to "smallpox."
• 1530 Italian physician/poet Hieronymus Fracastorius published *Syphilidis, sive Morbi Gallici*
• Shepherd “Syphilis”
• Accurate descriptions
Syphilis pandemic

- Early cases made people seriously ill
  - High death rates
- By 1500 - medical literature filled with case descriptions
- 1557 – “leper” colonies set up throughout Europe
- 1690 - syphilitic patients treated in hospitals
- Treatment of choice at this time was mercury
DRUGS

Syphilis - Evolution of therapy
Mercury

- Used to treat skin infections
  - 1025 - "The Canon of Medicine" by the Persian physician Avicenna
  - 1496 - Giorgio Sommariva of Verona treats syphilis
- Multiple routes of administration
- Oral, topical, ointment, fumigation
Mercury
Mercury

- Popular for three centuries
- 1800's - mercury used liberally to treat any ulcer
- Patients injured from the treatment
- Side effects:
  - tooth loss
  - skin and mouth ulcers
  - neurological damage
  - death
- “A night in the arms of Venus leads to a lifetime on Mercury.”
Cause Discovered

- Diagnosis originally relied on visible symptoms
- 1905 German microbiologists Schmudinn and Hoffman discovered the bacteria that cause syphilis
  - Used a modified Giemsa stain
- 1906-German researchers developed the Wassermann test
  - complement fixation
- Prevalence in European cities is high
- Now disease can be caught in asymptomatic stages
Paul Ehrlich

- 1909 new field of chemotherapy
- Used the phrase 'silver bullet'
Ehrlich finds cure for syphilis

- Tested 900 different compounds on mice
- Sahachiro Hata went back to #606
- Tested on mice, guinea pigs, and rabbits with syphilis
- Complete cures within three weeks
  - No dead animals!
- In 1910 the drug was released, called Salvarsan “Arsenic saves”
Salvarsan

- First chemotherapeutic agent
- Revolutionized the treatment of syphilis

- 1915 medical textbook:
  “Pregnant syphilitic women should be given four or five injections of salvarsan as soon as conception is known to have occurred, and mercury continued throughout pregnancy.”

Alexander Fleming

• First in England to administer Salvarsan intravenously
  • Such a busy practice he got the nickname "Private 606"

• World War I broke out
  • soldiers dying from:
    • Staphylococcal,
    • Streptococcal,
    • and pneumococcal infections

• Wanted a cure like Salvarsan

Penicillin discovered

- Began experimenting
- Mold *Penicillium*

- Presented his findings in 1929
  - British Journal of Experimental Pathology

Source: Alexander Fleming, "On the Antibacterial Action of Cultures of a Penicillium, with Special Reference to Their Use in the Isolation of B. Influenzas” The British Journal of Experimental Pathology, (1929)
Drug isolated

- World War II revitalized interest
- Howard Florey and Ernst Chain picked up the work
- Began experimenting with penicillium mold
- Injected live mice
- Then tried it on human subjects
- Could not make enough
- Recovered drug from urine
Mass production

- Florey traveled to the U.S.
- Agricultural research center Peoria, Illinois
  - used fermentation to grow *Penicillium*, fed by CORN
- *Penicillium* loved it - 500 times yield
- United States entered World War II
  - Recruited chemical companies
- By the time the war ended
  - 650 billion units a month
The cure

• World’s most effective, life saving drug
• 1943 - Use of penicillin to treat syphilis began
• Dramatic drop in prevalence
• Still used today
• Recommended treatment for 1’ and 2’ syphilis:
  • Benzathine penicillin G 2.4 million units IM in a single dose
MEDICAL THUGS

Research on vulnerable populations
Tuskegee

- 1932 - U.S. Public Health Service began a study
- “the Tuskegee Study of Untreated Syphilis in the Negro Male”
- 399 African-American men with syphilis
- 201 uninfected controls
- Originally 6 months…
Tuskegee

- No informed consent
- Told men they were treated for "bad blood"
- Free medical exams, meals, and burial insurance
- Local physicians assisted – denied treatment
- Penicillin became the drug of choice for syphilis in 1947
- Intentionally denied to subjects
- 1968 - Ethics of study criticized
- 1969 - CDC reaffirmed need for study
  - Supported by AMA and NMA local chapters
- 1972 - National press coverage…study ended
1997 Clinton Apology

• "To the survivors, to the wives and family members, the children and the grandchildren, I say what you know: No power on Earth can give you back the lives lost, the pain suffered, the years of internal torment and anguish.

• "What was done cannot be undone. But we can end the silence. We can stop turning our heads away. We can look at you in the eye and finally say, on behalf of the American people: what the United States government did was shameful.

• "And I am sorry."
Another study uncovered...

• John Charles Cutler
  • PHS researcher on Tuskegee study
• Led 1946 to 1948 study in Guatemala
• Sponsored by:
  • Public Health Service
  • National Institutes of Health
  • World Health Organization
  • Guatemalan government
Guatemala

- Used prostitutes to infect:
  - prison inmates
  - insane asylum patients
  - soldiers

- Infected people with:
  - "direct inoculations made from syphilis bacteria poured into the men's penises and on forearms and faces that were slightly abraded ... or in a few cases through spinal punctures"

- Approximately 1300 people were infected, including orphaned children

- The results were never even published...
Thomas Parran

- Cutlers’ supervisor, US Surgeon General
  - “You know, we couldn’t do such an experiment in this country.”
  - Did not put an end to it.
Guatemala

• Cutler chose to do the study in Guatemala
  • Would not fly in the US

• His superior, PHS physician R.C. Arnold:
  • “I am a bit, in fact more than a bit, leery of the experiment with the insane people. They can not give consent, do not know what is going on, and if some goody organization got wind of the work, they would raise a lot of smoke.”
Obama Administration Apology

- October 1, 2010: Hillary Clinton and HHS Secretary Kathleen Sebelius:
  - "Although these events occurred more than 64 years ago, we are outraged that such reprehensible research could have occurred under the guise of public health"

- April 2013:
  - American Sexually Transmitted Disease Association renamed "Thomas Parran Award" to "The ASTDA Distinguished Career Award."
Reaction

- Abuse of trust by medical profession
  - Raised severe controversy
- Major changes in how patients are protected
- 1979 Belmont Report
- Requirement for Institutional Review Boards
- Informed consent for all research subjects
DIAGNOSIS TODAY

Screening algorithms and tests
Diagnosis of syphilis

• Cannot be cultured
• 2 types of tests
  1. Non-treponemal tests
  2. Treponemal tests

• 2 algorithms:
  1. Traditional (CDC recommended)
  2. Reverse
Non-treponemal tests

- Rapid plasma reagin (RPR)
- Venereal Disease Research Laboratory (VDRL)
- Antigen is Cardiolipin
- Detects reagin
  - Antibodies against cardiolipin
- Catch active infection
- Monitor titers for therapy

- False positives with HIV, HSV, malaria, IV drug use, SLE, RA, pregnancy, leprosy, etc.
- Therefore follow up with confirmatory test.
RPR, VDRL

Agglutination reaction

Soluble Antigen, Antibody, and Chromogen

Antigen–Antibody Complex

Non reactive  Weakly reactive  Strongly reactive
Treponemal tests

- Fluorescent treponemal antibody absorbed (FTA-ABS)
- Treponema pallidum particle agglutination assay (TPPA)
- Enzyme immunoassays (EIAs)
- Chemiluminescence immunoassays (CIAs)

- Antigen is T. Pallidum
- Detects specific antibodies
- Positive for life
FTA-ABS

- Fluorescent treponemal antibody absorbed
- Antigen is whole bacteria
- “absorbent” - non-pathogenic treponeme
- Fluorophore-labeled secondary antibodies
- Lower specificity
  - SLE (lupus)
  - Pregnancy
  - Leprosy
- Subjective
- Not recommended
TPPA

- Treponema pallidum particle agglutination assay
- Gelatin particles sensitized with T. pallidum antigen
- Particles agglutinate with antibody, forming a mat
EIA/CIA

- Enzyme immunoassays (EIAs)
- Chemiluminescence immunoassays (CIAs)
- Qualitative detection of IgG antibodies to *T. pallidum*

**Pros:**
- Automated
- Low cost / high volume
- Can catch early syphilis

**Cons:**
- Treated vs untreated disease

**Recommended screening test in EU – reverse algorithm**
EIA or ELISA

Indirect ELISA

Antigen
Primary antibody
Enzyme-linked secondary antibody
2 Algorithms

Traditional (CDC)
- 1st non-treponemal test
- Confirm with treponemal test
- Detects active infection
- Can miss latent or treated infection

Reverse
- Begin with EIA/CIA
- Confirm with RPR
- Good for high throughput screening
- Catch latent/early infection
- Can’t differentiate treated from untreated
Syphilis serologic screening algorithms

**Traditional**
- Quantitative RPR
  - RPR+
    - TP-PA+ or other trep. test
      - TP-PA+ Syphilis (past or present)
      - TP-PA- Syphilis unlikely
  - RPR-

**Reverse sequence**
- EIA or CIA
  - EIA/CIA+
    - Quantitative RPR
      - RPR+
        - TP-PA+ Syphilis (past or present)
      - RPR-
        - TP-PA- Syphilis unlikely
  - EIA/CIA-

Back to our case…

Screening algorithm?

• VDRL followed by FTA-ABS
• Traditional

Treatment?

• Penicillin G, IM
Conclusion

- Syphilis has had a profound effect on:
  - Practice of medicine
  - Art, literature
  - Drug development
  - Laboratory medicine
  - Ethical research on human subjects
Questions?

Earliest known medical illustration of patients suffering from syphilis
Vienna, 1498
Famous People with Syphilis

• Hitler
  • 1908 - Contracted syphilis from a Jewish prostitute
  • Wrote extensively in *Mein Kampf* about the “Jewish disease”

• Others
  • Shakespear
  • Pope Alexander VI
  • Ivan the Terrible
  • Henry VIII
  • Hernan Cortez
  • Al Capone
Acknowledgements

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• Dr. Fred Strathman
• Dr. Deanna Fang
• Dr. Sara Nadiwanda
• Dr. Marc Couturier