Tropikal Hastalıklar: Kusbakısı
Tropical Infections: A Bird's Eye View

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Outline

• Origin of Tropical Medicine & current relevance
• Exotic tropical infections: a starter
• Recent achievements and challenges in TB
• Solving the mystery fever
British Empire: 1900

- British Empire - 531 million
- Qing Empire (China) - 432 million
- Russian Empire - 176 million
- Mughal Empire (India) - 175 million
- Ming Empire (China) – 160 million
- Ottoman Empire (Turkey) – 35 million

- Germ Theory & elimination of Climatic model
- Political and economic approach to empire
- Challenges of colonialism – ‘White man’s grave’
- Scientific Medicine - Tropical Medicine
Sir Patrick Manson: Father of Tropical Medicine

- ‘The role of the Society is to do justice to the tropical patients and to tropical diseases and hygiene’
- Sir Patrick Manson. Presidential address to Society of Tropical Medicine 1907
Challenges of Globalisation

Ebola

H1N1

SARS

What You Need to Know
The New Age of Epidemics
HIV Origin

- Unusual opportunistic infections noted in 1981
- Mutated virus from Central African monkey retrovirus
- Retrospective pathology search identified oldest known AIDS patient 1957
- SIV presumably transferred to humans during the late 19th or early 20th century
- Global travel
Tropical & Subtropical Regions
Common Tropical Infections

- Tuberculosis
- Malaria
- Dengue infection
- Rickettsioses:
  - Scrub typhus
  - Murine typhus
- Enteric fever
  - Typhoid fever
  - Paratyphoid fever
- Leptospirosis
- Melioidosis
- Anthrax
- Helminthic infections
- Leishmaniasis
- Infective diarrhea
- Tick borne viral diseases
An Interesting Case

- 49 year old man, a farmer
- No known co-morbid illnesses
- 3 days history of
  - Fever
  - Headache – severe
  - Dry cough
- Day of admission: 2 episodes of generalized seizures and altered sensorium
Physical examination

- Unconscious; GCS 8/15
- Temp-101°F, HR-110/min; BP-120/70mmHg; RR: 30/min
- No pallor / clubbing / cyanosis
- CVS: Normal
- RS: Clear
- P/A: Soft; no hepatosplenomegaly
- CNS:
  - GCS 8/15
  - Signs of meningeal irritation +
  - Pupils- equal and reacting to light
  - No focal deficits noted
  - Bilateral extensor plantars
# Investigations

<table>
<thead>
<tr>
<th>WBC</th>
<th>9500 /cumm (N 84, L7 M9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>14.7 gm/dl</td>
</tr>
<tr>
<td>PLT</td>
<td>90,000/cumm</td>
</tr>
<tr>
<td>Na</td>
<td>135 mmol/l</td>
</tr>
<tr>
<td>K</td>
<td>3.5 mmol/l</td>
</tr>
<tr>
<td>Cr</td>
<td>1.0 mg/dl</td>
</tr>
<tr>
<td>T. bilirub</td>
<td>0.7 mg/dl</td>
</tr>
<tr>
<td>D. bili</td>
<td>0.5 mg/dl</td>
</tr>
<tr>
<td>T. prot</td>
<td>6.9 g%</td>
</tr>
<tr>
<td>Alb</td>
<td>3.6 g%</td>
</tr>
<tr>
<td>SGOT</td>
<td>70U/L</td>
</tr>
<tr>
<td>SGPT</td>
<td>25 U/L</td>
</tr>
<tr>
<td>Alk. phos</td>
<td>93U/L</td>
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</tbody>
</table>

HIV ELISA - Negative
CSF analysis:
• WBC - 5000 cells (P80,L20); RBCs-4800 cumm
  Protein- 636 mg/dl;
  Sugar – 89 mg/dl
  RBS: 120 mg/dl
CSF & Blood Culture: *Bacillus anthracis*
Human Transmission

• Cutaneous
  – Contact with infected tissues, wool, hide, soil
• Inhalational
  – Tanning hides, processing wool or handling carcases
• Gastrointestinal
  – Undercooked meat
The Organism

- *Bacillus anthracis*
- Large, gram-positive, non-motile bacilli
- Two forms
  - Vegetative
  - Spore
- Over 1,200 strains
- Nearly worldwide distribution
Anthrax Epidemiology

http://www.vetmed.lsu.edu/whocc/mp_world.htm
Inhalational Anthrax

• Incubation: 1 to 7 days
• Initial phase
  – Nonspecific (mild fever, malaise)
• Second phase
  – Severe respiratory distress
  – Dyspnoea, stridor, cyanosis, mediastinal widening, death in 24 to 36 hours
• Case fatality: 75 to 90%
How does this kill the individual?
# Treatment for Systemic Anthrax with Meningitis

<table>
<thead>
<tr>
<th>Preferred</th>
<th>Alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. A Bactericidal Agent (Fluoroquinolone)</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin 400 mg every 8H</td>
<td>Levofloxacin, Moxifloxacin</td>
</tr>
<tr>
<td>2. A Bactericidal Agent (β-lactam)</td>
<td></td>
</tr>
<tr>
<td>Meropenem 2 g every 8H</td>
<td>Imipenem Penicillin</td>
</tr>
<tr>
<td>3. A Protein Synthesis Inhibitor</td>
<td></td>
</tr>
<tr>
<td>Linezolid 600 mg every 12H</td>
<td>Clindamycin</td>
</tr>
</tbody>
</table>

Tuberculosis – A Global Emergency

• 2 billion people are infected with *M. tb*
• 1.7 million people die/year
• Nearly half a million cases of Multi-Drug Resistant-TB/ year
TB Diagnosis

- **Microscopy** 1882
- **Culture** 1882
- **Chest X-ray** 1896
Mycobacterial Culture

- **Manual:**
  - Solid egg based: L.J
  - Agar based Middlebrook 7H10 / 11
  - Liquid based: Middlebrook 7H9

- **Automated:**
  - BACTEC 460 TB (CO2 production)
  - MGIT 960 (O2 utilisation)
  - MB Bact (CO2 production)
GeneXpert® MTB/RIF Test

Workflow
- sputum
- simple 1-step external sample prep. procedure
- time-to-result < 2 h
- throughput: ≥ 16 tests/day/module
- no need for biosafety cabinet
- integrated controls
- true random access

Performance
- specific for MTB
- sensitivity better than smear, similar to culture
- detection of rif-resistance via rpoB gene

Product and system design
- test cartridges for GeneXpert System
- several GeneXpert modules can be combined in 1 workstation
- swap replacement of detection unit
- ~1 day technician training for non-mycobacteriologists
Xpert MTB/RIF: Integration of technologies

- Molecular beacons
- RT PCR
- Resistance associated mutations
- Fluorimetric probes
- Microfluidics
- Sonic bacterial lysis

Real Time PCR

Microfluidics

TB DNA sequence
<table>
<thead>
<tr>
<th>Site and Total</th>
<th>Phenotypic Drug-Susceptibility Testing†</th>
<th>Phenotypic Drug-Susceptibility Testing and Discrepant Resolution by Sequencing†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity for Rifampin Resistance</td>
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</tr>
<tr>
<td></td>
<td>Specificity for Rifampin Resistance</td>
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</tr>
<tr>
<td>Lima, Peru — no./total no. (%)</td>
<td>16/16 (100.0)</td>
<td>190/193 (98.4)</td>
</tr>
<tr>
<td>Baku, Azerbaijan — no./total no. (%)</td>
<td>47/49 (95.9)</td>
<td>90/94 (95.7)</td>
</tr>
<tr>
<td>Cape Town, South Africa — no./total no. (%)</td>
<td>15/16 (93.8)</td>
<td>126/126 (100.0)</td>
</tr>
<tr>
<td>Durban, South Africa — no./total no. (%)</td>
<td>3/3 (100.0)</td>
<td>38/38 (100.0)</td>
</tr>
<tr>
<td>Mumbai, India — no./total no. (%)</td>
<td>119/121 (98.3)</td>
<td>61/64 (95.3)</td>
</tr>
<tr>
<td>Total for rifampin resistance</td>
<td><strong>200/205 (97.6)</strong></td>
<td><strong>505/515 (98.1)</strong></td>
</tr>
<tr>
<td>Correct — no./total no. (%)</td>
<td>94.4–99.0</td>
<td>96.5–98.9</td>
</tr>
<tr>
<td>95% CI — %</td>
<td></td>
<td></td>
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<tr>
<td>Total for multidrug resistance</td>
<td>195/200 (97.5)</td>
<td>197/199 (99.0)</td>
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<tr>
<td>Correct — no./total no. (%)</td>
<td>94.3–98.9</td>
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Genotypic tests: Hain Line Probe Assay (LPA)

1) DNA Extraction

2) DNA Amplification by PCR

3) Hybridization

4) Evaluation
Conjugate Control
Amplification Control
*M. tuberculosis* complex

*rpoB* Locus Control
*rpoB* wild type probe 1
*rpoB* wild type probe 2
*rpoB* wild type probe 3
*rpoB* wild type probe 4
*rpoB* wild type probe 5
*rpoB* wild type probe 6
*rpoB* wild type probe 7
*rpoB* wild type probe 8
*rpoB* mutation probe 1
*rpoB* mutation probe 2A
*rpoB* mutation probe 2B
*rpoB* mutation probe 3

*katG* Locus Control
*katG* wild type probe
*katG* mutation probe 1
*katG* mutation probe 2

*inhA* Locus Control
*inhA* wild type probe 1
*inhA* wild type probe 2
*inhA* mutation probe 1
*inhA* mutation probe 2
*inhA* mutation probe 3A
*inhA* mutation probe 3B
colored marker

Resistance
- R+I I R+I R+I

R = Rifampicin
I = Isoniazid
<table>
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<tr>
<th>Year</th>
<th>Technology</th>
<th>Turnaround time</th>
<th>Sensitivity gain</th>
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| Before 2007 | ZN microscopy  
Solid Culture | 2 days  
30-60 days | Baseline |
| 2007     | Liquid Culture  
Rapid speciation | 15-30 days      | +10% compared to LJ |
| 2008     | Line Probe Assay                   | 2-4 days               | At this time for S+ only |
| 2009     | LED-based FM                        | 1-2 days               | + 10% compared to ZN |
| 2010     | Integrated NAAT  
(TB, Rif) | 90 minutes             | + 40% compared to ZN |
Hand held Portable devices in development

TrueLab NAAT by Molbio Diagnostics Private Ltd., India

Genedrive technology by Epistem Ltd, Manchester, UK
Unusual Acute Febrile Illness in 90s

- Acute febrile illness with multiple organ involvement

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<td>Alk. ph</td>
<td>156</td>
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CSF: WBC – 65; (P 2, L 98)
Protein – 103; Glucose – 56
Scrub Typhus

- A mite-borne, zoontoic bacterial infection
- Causative agent: *Orientia tsutsugamushi* (*Rickettsia tsutsugamushi*)
- Three major serotypes – Kato, Karp & Gilliam
- Manifests as fever and multiorgan involvement.
- Vector: chiggers (larva of trombiculid mite - *Leptotrombidium*)
- Reservoir: chiggers & rats
  - Normal cycle: rat to mite to rat
  - Transovarian transmission
- Humans incidentally infected
When should scrub typhus be suspected?

• Undifferentiated febrile illness with:
  – Pathognomonic eschar
  – Evidence of multisystem involvement, especially with:
    - Transaminase elevation
    - Thrombocytopenia
    - Leukocytosis

Varghese et al. J Infection 2006; 52:56–60
Organ Involvement & Complications

- ARDS - 44%
- Respiratory involvement (breathlessness / pneumonitis) in >60%
- Hepatic involvement >80%
- Refractory shock – 25%
- Aseptic meningitis or meningoencephalitis – 19%
- Renal dysfunction – 13%
- MODS – 38%

• 137 scrub typhus patients and 134 controls
• PCR restriction fragment length polymorphism
• Significant heterozygous TLR4 - Asp299Gly among cases
Cytokine Network in Scrub Typhus: High Levels of Interleukin-8 Are Associated with Disease Severity and Mortality

Elisabeth Astrup1,2*, Jeshina Janardhanan3, Kari Otterdal2,4, Thor Ueland2,4, John A. J. Prakash5, Tove Lekva2,4,6, Øystein A. Strand7, O. C. Abraham3, Kurien Thomas8, Jan Kristian Damås9,10, Prasad Mathews8, Dilip Mathai8, Pål Aukrust2,4,11, George M. Varghese3

- Cytokine profile and their relation to disease severity and clinical outcome
- 129 ST patients compared to 31 healthy controls and 31 infectious disease controls
- IL-8, monocyte chemoattractant peptide-1 and macrophage inflammatory protein-1b were associated with disease severity and mortality
- Platelet-derived mediators – RANTES decreased
Molecular Detection & Sequencing of *O. tsutsugamushi*

- Kato-like – 61%
- Karp-like – 28%
- Gilliam – 2%

Varghese GM et al. Emerg Infect Dis. 2015
Acute Febrile Illness – CMC Vellore

(398 patients)

- Scrub Typhus (189)
- Malaria (68)
- Enteric Fever (32)
- Dengue (28)
- Leptopirosis (12)
- Spotted Fever (7)
- Hantan virus (1)
- Alternate Diagnosis (29)
- Unclear Diagnosis (32)

Summary

• The dramatic emergence of tropical infections underscores the ease with which pathogens can move between countries and continents via today’s modern transportation.

• These requires more than local geographic considerations with more universal etiology of infectious agent, reservoir, and vector.

• It is an intellectually challenging and rapidly changing area of Infectious Diseases.
Thank You