TB, West Nile Disease, and Influenza A

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Disclosures
Edward A. Dominguez, MD

- Research
  - Cubist
- Consultancy
  - Pfizer
  - Celgene
- Speaker Bureau
  - Astellas
  - Cubist
  - Pfizer
What I hope to achieve...

- Tuberculosis update
  - Epidemiology
  - Quantiferon vs. PPD
  - Therapy
- West Nile update
  - What we learned from 2012
- Influenza A update
  - Seasonal and pandemic
  - Treatment
  - Vaccines
What I Hope to Avoid!!!!
Tuberculosis
Epidemiology of Tuberculosis

- One-third of the world population is infected with TB
- 9 million new cases and 1.4 million deaths annually worldwide
- Most U.S. cases are in urban and immigrant communities
- Among immigrants to US, TB is largely caused by reactivation of latent infection.
- Among US natives, many cases result from recent transmission.
Primary Tuberculosis and Sequelae

- Primary TB usually a self-limited, mild pneumonic illness; often undiagnosed
- The incidence of progression from latent to active infection is ~5% in the first 5 years, plus an additional 5% lifetime risk thereafter
Reported TB Cases
United States, 1982–2011

No. of Cases


Year

10,528
TB Case Rates,* United States, 2011

*Cases per 100,000.
Conditions That Increase Risk of Progression to TB

- HIV (risk of TB disease is ~10% each year)
- CXR suggestive of previous untreated TB
- Diabetes mellitus
- Silicosis
- Prolonged immunosuppressive therapy
- Cancer of the head and neck
- Hematologic and RES diseases
- End-stage renal disease
- Intestinal bypass or gastrectomy
- Malabsorption syndromes
- Low body weight (10% or more below the ideal)
Risk Factors for Drug-Resistant TB

- History of treatment with TB drugs
- Contacts of persons with drug-resistant TB
- Foreign-born persons from high prevalence drug-resistant areas
- Smears or cultures remain positive despite 2 months of TB treatment
- Received inadequate treatment regimens for >2 weeks
MTB: Diagnosis of LTBI

Testing methods

- Tuberculin skin test (TST):
  - 0.1 mL purified protein derivative (PPD)
  - In HIV-infection, positive is induration $\geq 5$ mm at 48-72 hours
  - Specificity 56-95%

- Interferon-gamma release assay (IGRA):
  - IFN-$\gamma$ release in response to MTB-specific peptides
  - Sensitivity: 0.70 to 0.90 (T-Spot more sensitive)
    - PPD test is about 0.76
  - Specificity:
    - Non-BCG vaccinated: 0.99
    - BCG-vaccinated: 0.93 to 0.96
    - PPD is only 0.56
  - Advanced immunosuppression may cause false-negative results to both tests
MTB: Treatment of TB Disease

For drug-susceptible pulmonary TB

- Two phases:
  - Initial: 2 months
    - Isoniazid (INH), rifampin (RIF) or rifabutin (RFB), pyrazinamide (PZA), ethambutol (EMB)
    - If organism is susceptible to INH, RIF, and PZA, may discontinue EMB
  - Continuation: 4 months
    - INH + RIF (or RFB)
MTB: Monitoring

- Close follow-up is essential to ensure treatment success
- Pulmonary TB: ≥1 sputum smear and culture monthly until 2 consecutive specimens are negative on culture
  - Positive cultures after 3 months of treatment: repeat drug susceptibility tests
  - Positive cultures after 4 months: consider as treatment failure; manage accordingly
- Extrapulmonary TB: follow-up evaluation depends on sites involved
Treatment of Multi-drug Resistant TB

- Best regimens include all of the following:
  - Aminoglycoside (streptomycin or amikacin) or capreomycin
  - Fluoroquinolone
  - Four other agents to which the isolate is sensitive
- Treat for 24 months after culture conversion
- Always use observed therapy
- Delamanid (not yet approved)
- Linezolid (not FDA-approved for this)

West Nile Virus, 2012

- Virology
- Epidemiology
  - Transmission
  - 2012 Epidemic
  - MHS experience
- Clinical syndromes
- Management and Prevention
West Nile Virus

- Family: *Flaviviridae*
- Genus: *Flavivirus*
- Japanese encephalitis group
  - Japanese encephalitis virus
  - Murray Valley encephalitis virus
  - St. Louis encephalitis virus
  - Usutu virus
  - *West Nile virus* (Kunjin virus)
- Arboviruses (arbo = arthropod borne)
Potential Hosts of West Nile Virus

- At least 225 species of birds
- At least 49 species of mosquito
- At least 28 species of mammals, inc. cats, dogs, sheep, llama, wolf, goats, squirrels, skunks, etc...
- Alligators.....
West Nile Virus Transmission Cycle

- Mosquito vector
- Incidental infections
- Bird reservoir hosts
- West Nile virus
WNV: Novel Modes of Transmission

- Blood transfusion-associated transmission
  - As of July 2003, US blood donors screened for WNV using nucleic acid amplification testing (NAT)

- Solid organ transplant transmission
  - 7 cases as of 2009

- Intrauterine transmission
  - Ongoing CDC registry; only 1 proven case

- Transmission through breast milk
  - Only 1 proven case
WNV Human Infection “Iceberg”

- Asymptomatic Infection
  - Generation of life-long immunity (presumed)

Incubation: 3-14 days

- <1% CNS disease
- ~20% "West Nile Fever"
- ~80% Asymptomatic
Asymptomatic (~80%)  
- CNS disease (<1%)  
- "West Nile Fever" (~20%)  
- West Nile Fever  
  - Fever, headache, rash, fatigue
WNV Human Infection “Iceberg”

- <1% CNS disease
- ~20% “West Nile Fever”
- ~80% Asymptomatic

WNV Neuroinvasive Disease (WNND)
- Meningitis, encephalitis, poliomyelitis, Parkinson’s
West Nile Neuroinvasive Disease

“Meningitis”: Inflammation of the covering of the brain

“Encephalitis”: Inflammation of the brain itself

“Meningoencephalitis”

“(Polio)Myelitis”: Inflammation of the spinal cord
Methodist Health System 2012 WNV Experience

- Dallas: 8
- Charlton: 10*
- Mansfield: 16
- Richardson: 7

- Most cases: fever; meningitis

* One death: encephalitis, 10-day stay in ICU
Source: Dr. Zakir Shaikh, Med Director Infection Control, MHS
WNV: The Other “Iceberg”

Acute WNV Illness

WNV Long-term effects:
- Neurologic
- Kidney
WNV Post-infection Time Table

- **Stage-I**: IDNAT- MPNAT- IgM-
- **Stage-II**: IDNAT+ MPNAT- IgM-
- **Stage-III**: MPNAT+ IgM-
- **Stage-IV**: IDNAT+ MPNAT- IgM+
- **Stage-V**: IDNAT +/- MPNAT- IgM+/IgG+

Graph showing:
- WNV RNA (gEq per mL)
- Days post infectious mosquito bite
- RNA peak at ~7 days
- IgM and IgG markers
WNV Treatment

- Treatment
  - Most cases: manage the symptoms
  - Severe cases:
    - Polyclonal IVIG
    - NIH-sponsored randomized, placebo-controlled trial of high-titer WNV intravenous immune globulin (IVIG)

Beasley DW. *Immunotherapy* 2011;3:269-85
WNV Prevention

- WNV human vaccine
  - Phase I / II clinical trials
  - Promising safety, efficacy profiles

- Prevention
  - Avoid outdoors at dusk and dawn
  - Drain standing water
  - DEET
The Clinical Impact of WNV Infection
1999: What We Thought We Knew...

- Most WNV infections benign
- Febrile illness benign and mild
- Severe encephalitis associated with older age
- Infection acquired through bite of infected mosquitoes
- Neurologic illness from WNV: meningitis and encephalitis
The Clinical Impact of WNV Infection
2012: What We Know Now...

- Most WNV infections benign (fortunately)
- Febrile illness generally mild, but may be associated with fatigue and cognitive problems
- Severe encephalitis associated with older age, but also immunosuppression
- Infection acquired through bite of infected mosquitoes, but also blood transfusion, solid organ transplantation, intrauterine (rarely)
- Neurologic illness from WNV: meningitis and encephalitis, poliomyelitis, parkinsonism
Influenza Viruses

- RNA virus
- *Orthomyxoviridae* family
- Types A, B or C based on antigenic differences of their nucleo- and matrix proteins
- Avian influenza viruses (AIV) belong to type A
- On the basis of the antigenicity of these glycoproteins, influenza A viruses currently cluster into sixteen H (H1 - H16) and nine N (N1 - N9) subtypes.
Circulating Influenza Viruses

- **Seasonal influenza**
  - A(H3N2), A(H1N1), B

- **Avian influenza** (‘bird flu’)
  - A(H5 and H7, e.g. HPAI H5N1)

- **Swine influenza** (‘swine flu’) -> variant flu
  - A(H1N1v) - 2009 pandemic strain
  - A(H3N2v) – 2011-2012 US strain
Influenza Positive Tests Reported to CDC, National Summary, 2012-13 Season, weeks ending Jan 19, 2013 - Feb 08, 2013
Reported by: U.S. WHO/INRVSS Collaborating Laboratories

Number of Influenza Positive Tests
- A (H1) - 0
- A (Unable to Subtype) - 0
- A (H3) - 4366
- 2009 H1N1 - 262
- A (Subtyping not Performed) - 2841
- B - 2513
- H3N2v - 0
- No Data
Data from the Influenza Hospitalization Surveillance Network (FluSurv-NET), a population-based surveillance for influenza related hospitalizations in children and adults in 15 US states. Incidence rates are calculated using the National Center for Health Statistics’ (NCHS) population estimates for the counties included in the surveillance catchment area.
### Laboratory-Confirmed Influenza Hospitalizations

**Preliminary data as of Feb 09, 2013**

<table>
<thead>
<tr>
<th>Medical Condition</th>
<th>Pediatric Cases</th>
<th>Adult Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asthma</strong></td>
<td>5.6%</td>
<td>16.7%</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>0.8%</td>
<td>37.3%</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>0.8%</td>
<td>24.8%</td>
</tr>
<tr>
<td>Immune suppression</td>
<td>0.3%</td>
<td>13.5%</td>
</tr>
<tr>
<td>Metabolic disorder</td>
<td>2.7%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Neurologic disorder</td>
<td>12.7%</td>
<td>16.1%</td>
</tr>
<tr>
<td>Neuromuscular disorder</td>
<td>1.9%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Obesity</td>
<td>0.1%</td>
<td>28.2%</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>18.8%</td>
<td>29.7%</td>
</tr>
<tr>
<td>Renal disease</td>
<td>1.5%</td>
<td>14.9%</td>
</tr>
<tr>
<td>No known condition</td>
<td>5.3%</td>
<td>43.6%</td>
</tr>
</tbody>
</table>

**Asthma** includes a medical diagnosis of asthma or reactive airway disease. **Cardiovascular diseases** include conditions such as coronary heart disease, cardiac valve disorders, congestive heart failure, pulmonary hypertension, and aortic stenosis. Does not include hypertension disease only. **Chronic lung diseases** include conditions such as bronchiolitis obliterans, chronic aspiration pneumonia, and interstitial lung disease. **Immune suppression** includes conditions such as immunoglobulin deficiency, leukemia, lymphoma, HIV/AIDS, and individuals taking immunosuppressive medications. **Metabolic disorders** include conditions such as diabetes mellitus, thyroid dysfunction, adrenal insufficiency, and liver disease. **Neurologic diseases** include conditions such as seizure disorders, cerebral palsy, and cognitive dysfunction. **Neuromuscular diseases** include conditions such as multiple sclerosis and muscular dystrophy. **Obesity** was assigned if indicated in patient’s medical chart or if body mass index (BMI) > 30 kg/m². **Pregnancy** percentage calculated using number of female cases aged between 15 and 44 years of age as the denominator. **Renal diseases** include conditions such as acute or chronic renal failure, nephrotic syndrome, glomerulonephritis, and impaired creatinine clearance. **No known condition** indicates that the case did not have any known underlying medical condition indicated in medical chart at the time of hospitalization. Only includes cases for which data collection has been completed through the medical chart review stage.
Avian Influenza Viruses

Kaye and Pringle 2005
Countries with H5N1 Human Cases
Virologic Diagnosis

– Culture
– Antigen detection (Rapid tests, ELISA, IFA)
– RT-PCR
– Serology

– All studies more likely to be positive if collected in first 3 days of illness
<table>
<thead>
<tr>
<th>Antiviral Agent</th>
<th>Activity Against</th>
<th>Use</th>
<th>FDA Approved For</th>
<th>Not Recommended for Use in</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oseltamivir (Tamiflu®)</td>
<td>Influenza A and B</td>
<td>Treatment</td>
<td>2 wks and older</td>
<td>N/A</td>
<td>Adverse events: nausea, vomiting, Sporadic, transient neuropsychiatric events (self injury or delirium) mainly reported among Japanese adolescents and adults.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemoprophylaxis</td>
<td>1 yr and older</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Zanamivir (Relenza®)</td>
<td>Influenza A and B</td>
<td>Treatment</td>
<td>7 yrs and older</td>
<td>people with underlying respiratory disease (e.g., asthma, COPD)</td>
<td>Allergic reactions: oropharyngeal or facial edema. Adverse events: diarrhea, nausea, sinusitis, nasal signs and symptoms, bronchitis, cough, headache, dizziness, and ear, nose and throat infections.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemoprophylaxis</td>
<td>5 yrs and older</td>
<td>people with underlying respiratory disease (e.g., asthma, COPD)</td>
<td></td>
</tr>
<tr>
<td>Vaccine</td>
<td>Trade name</td>
<td>Manufacturer</td>
<td>Presentation</td>
<td>Mercury content (µg Hg per 0.5 mL dose)</td>
<td>Ovalbumin content (µg per 0.5mL dose)</td>
</tr>
<tr>
<td>------------------</td>
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<td>--------------------------------------</td>
</tr>
<tr>
<td>TIV</td>
<td>Fluzone</td>
<td>Sanofi Pasteur</td>
<td>0.25 mL prefilled syringe</td>
<td>0.0</td>
<td>&lt;0.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.5 mL prefilled syringe</td>
<td>0.0</td>
<td>—5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.5 mL vial</td>
<td>0.0</td>
<td>—5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.0 mL multidose vial</td>
<td>25.0</td>
<td>—5</td>
</tr>
<tr>
<td>TIV</td>
<td>Agriflu****</td>
<td>Novartis Vaccines</td>
<td>0.5 mL prefilled syringe</td>
<td>0</td>
<td>&lt;0.4</td>
</tr>
<tr>
<td>TIV</td>
<td>Fluvirin</td>
<td>Novartis Vaccines</td>
<td>0.5 mL prefilled syringe</td>
<td>≤1</td>
<td>≤1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5.0 mL multidose vial</td>
<td>25.0</td>
<td>≤1</td>
</tr>
<tr>
<td>TIV</td>
<td>Fluarix</td>
<td>GlaxoSmithKline</td>
<td>0.5 mL prefilled syringe</td>
<td>0</td>
<td>≤0.05</td>
</tr>
<tr>
<td>TIV</td>
<td>FluLaval</td>
<td>ID Biomedical Corporation of Quebec (distributed by GlaxoSmithKline)</td>
<td>5.0 mL multidose vial</td>
<td>&lt;25.0</td>
<td>≤0.3</td>
</tr>
<tr>
<td>TIV</td>
<td>Afluria</td>
<td>CSL Biotherapies (distributed by Merck)</td>
<td>0.5 mL prefilled syringe</td>
<td>0.0</td>
<td>≤1</td>
</tr>
<tr>
<td>TIV high-dose‡‡</td>
<td>Fluzone High-Dose</td>
<td>Sanofi Pasteur</td>
<td>0.5 mL prefilled syringe</td>
<td>0.0</td>
<td>&lt;5</td>
</tr>
<tr>
<td>TIV intradermal‡¶</td>
<td>Fluzone Intradermal</td>
<td>Sanofi Pasteur</td>
<td>0.1 mL prefilled microinjection system</td>
<td>0.0 (per 0.1 mL)</td>
<td>&lt;5</td>
</tr>
<tr>
<td>LAIV</td>
<td>FluMist***</td>
<td>MedImmune</td>
<td>0.2 mL prefilled intranasal sprayer</td>
<td>0.0 (per 0.2 mL)</td>
<td>&lt;0.24 (per 0.2mL)</td>
</tr>
</tbody>
</table>

* Data from the CDC.
Re-Emerging Infectious Diseases

- Malaria
- Tuberculosis, drug resistant
- Cholera
- Invasive Group A streptococci
- Diphtheria
- Pertussis – ongoing epidemic in NY NOW!
- Syphilis – increasing rates in Bay Area
- Dengue fever
Resources for Emerging Infectious Diseases

- Public Health Laboratories of the Ohio Department of Health, www.odh.state.oh.us/Resources/MultiMedia/EI_Slide/EIMAIN.HTM
Only One Flight Away from a Global Microbial Threat
Behind Mask
Thank You! 