Tuberculosis and Drug Resistance

“In South Africa, XDR TB and HIV Prove a Deadly Combination” – Robert Koenig 2008

“Tuberculosis control: the Relevance of Classical Principles in an Era of Acquired Immunodeficiency Syndrome and Multidrug Resistance”
Katherine Kaye and Thomas R. Frieden 1996
Kay and Frieden 1996

- Review paper (1996)
  - Summarize findings of recent epidemiological papers on TB resurgence and emergence of MDR strains
  - Implications for TB prevention and control
  - NYC Bureau of Tuberculosis Control
    - Response to city epidemic
  - Review critical gaps in knowledge and ability to control epidemic
In South Africa, XDR TB and HIV Prove a Deadly Combination” – Robert Koenig 2008

- South Africa – site of the largest XDR TB outbreak to date
- Co-infection with HIV complicates Tx
- Complex medical, ethical, and scientific issues in South Africa
Definitions

• MDR-TB: disease caused by *M. tuberculosis* resistant to isoniazid and rifampin
  – Primary: patient not on TB Tx infected by drug-resistant bacilli
  – Secondary (acquired): patient initially on drug-susceptible TB developed drug-resistant TB due to inappropriate or inadequate TX

• XDR-TB: Extensive drug-resistant tuberculosis
Natural History of TB

• Tuberculosis Infection
  – Most result from inhalation of airborne droplets
  – Undiagnosed, untreated smear positive patient – estimated to infect 10-14 persons a year
  – Bacille Calmette Guerin (BCG) vaccine variable and partial
    • May be effective protection against disseminated and meningeal TB in children
Natural History of TB

- Risk of disease progression
  - 10% of infected develop disease at some point in lives (most do so w/i 2 years of infection)
  - Young children likely to progress to dz after infxn
- Host characteristics
  - HIV infection
  - Fibrotic lung lesions
  - Silicosis
  - Some malignancies
  - Hemophilia
  - Immunosuppressive medical Tx
  - Low body weight
  - Diabetes
  - Heavy smoking
  - Certain genotypes
Natural History of TB

• Effect of treatment on natural history of TB
  – w/o Tx case fatality rate 50-60%
  – TB meningitis and military TB = 100% case fatality rate
  – Tx requires min. 6 months
  – Appropriate Tx and fully compliant patients, cure rates exceed 95% (drug-sensitive TB)
Economic Impact of TB in U.S.

• Economic Impact
  – US (1992) – average hospital cost per TB patient ~ $25,000
  – MDR-TB patients ~ $100,000 for inpatient care
  – Heavy burden on adults during productive years
  – Expensive treatments for MDR-TB may cripple TB programs in developing countries (back to pre-antibiotic era as individuals can’t be treated)
Recent epidemiology in U.S.

- Incidence of TB
  - Annual number of cases declined in general since 1953 (first data collected)
  - Dip in 1985 (22,201 cases)
  - 1985 to 1992 – increase in cases (26,673 in 1992)
    - Upsurge of TB in large cities
    - Shift in age distribution from elderly to 25-44 yrs
      - HIV infection
      - Young adult immigrants and refugees
    - 1993 – national number of cases declined annually

http://encarta.msn.com/media_461520261_761576449_-1_1/incidence_of_tuberculosis_united_states.html
• Reasons for reemergence of TB
  – Host susceptibility
    • HIV infection
      – Noted correlation of TB incidence and AIDS
      – Higher frequency of extrapulmonary TB
      – Increased risk for developing active TB
        » Increased risk of reactivation of latent TB
        » Rapid progression to active TB
        » Increased risk of exogenous reinfection
    • Substance abuse (injecting drug use, alcohol)
• Reasons for reemergence of TB
  – Population migration
    • Migration from areas of relatively high TB to areas of relatively low TB prevalence
    • In U.S. (1986-1993) – increased number and proportion of foreign-born TB cases
      – CA – Prop 187
        » Deny nonemergency care to undocumented immigrants (report to gvt officials)
        » Legislation may lead to increased TB M/M
    • Large populations of dislocated, malnourished ppl in crowded living conditions
• Reasons for reemergence of TB
  – Living conditions
    • Homelessness
      – H. in America exacerbated by deinstitutionalization of mentally ill, increased scarcity of jobs for unskilled, drug abuse
      – TB transmission and large shelters
        » NYC shelter-based clinic – 42.8% men infected, 6% had active TB
        » Transmission in Boston shelter – phage-typing of *M. tb* cultures – exogenous reinfection rather than reactivation
    • Correctional settings
      – Poorly ventilated, crowded
      – Inmates increased risk for infection (HIV, substance abuse, homelessness)
      – Frequent movt. Within and between facilities
    • Urbanization
• Reasons for reemergence of TB
  – Public health programs and medical practices
    • Dismantled TB control programs
      – Cuts in public health expenditures in NYC
      – 11% rate of therapy completion
    • Neglected sound infection control practices
      – Medical mismanagement of pts with MDR-TB
        » Late dx, tx with drugs that TB organisms already resistant to, failure to administer by DOT
      – Failure to make adequate use of tuberculin skin testing
      – Failure to follow up with preventive therapy
Drug resistance

• Development of drug resistance
  – Spontaneous single step mutation in *M. tuberculosis*
  – Low adherence rates to drug regimens
  – Availability of anti-TB drugs w/o Rx
  – MDR-TB patients require at least 18 months Tx (more costly, may be more likely to relapse)
XDR TB (Koenig 2008)

• XDR TB resistant to most second line drugs
  – Few options to treat other than older drugs and novel drug combinations

• DOTS protocol may not be the best approach in high-TB incidence areas
  – More investigations needed to determine best mixture of drugs to combat MDR and XDR TB in different regions

• Most XDR TB may go undiagnosed and unreported
  – WHO estimation ~ 27,000 people a year in 41 countries
XDR TB in South Africa (Koenig 2008)

• Medical challenges
  – Treating infections when “last-ditch” meds are resisted
  – Finding best ways to prevent hospital transmission

• Research challenges
  – ID new drug targets, rapid diagnostics
  – Investigating molecular evolution

• Ethical challenges
  – Extent that hospitals should isolate these patients against their will
  – Life-saving yet toxic drugs for many years?
Recent Epidemiology – MDR-TB

– 1960s and 1970s – relatively low numbers
  • Variation. Highest levels of primary drug resistance among Asian and Hispanic patients

– 1988 to 1990 – resurgence of MDR-TB
  • Among HIV-infected persons in several hospitals
  • High mortality rate (approx. 70%)

– Drug susceptibility patterns collected (CDC – National Action Plan to Combat MDR-TB)
International Trends in TB

- TB rates higher in eastern Europe and former Soviet Union than in west; rate of decline slowed in general
- TB remains leading cause of mortality and morbidity in developing countries
- Sub-Saharan Africa – HIV epidemic lead to dramatic increase in rates of TB
- Increased rates of acquired and primary drug resistance
- XDR-TB outbreak in South Africa in 2006 (Koenig 2008)
Implications for control

• Effective treatment of active disease
  • Detection and treatment of persons with active smear positive disease
  • Short-course therapy more cost-effective; patients more likely to complete

• Directly Observed Therapy
  • Reduces emergence of resistance
  • DOTS promoted by WHO (short course) to prevent TB mortality
Implications for control

- **Screening and prevention**
  - Preventive therapy documented to be highly effective
  - Therapy complicated with drug-resistance
    - Need to look at risk of developing active disease vs. risk of MDR-TB
  - Resources must be prioritized
  - Preventive therapy appropriate for HIV-infected persons
  - HIV-infected persons should not be housed near persons with TB
- **Improved screening and Tx services for immigrants and refugees**
  - Overseas screening
  - Reduction of rates should still be accomplished overseas
- **Surveillance**
  - Population-based surveillance
    - Can improve case management
    - Allow accurate monitoring of trends in TB and MDR-TB
    - Should include susceptibilities of *M. tb*
New York City Case Study

• The Tuberculosis Epidemic in New York City: Analysis and Response
  – 1991 survey of *M. tb* showed increased proportion of drug resistant isolates since 1983
  – NYC response – strengthened surveillance operations
    • susceptibility test reporting to health department
    • active surveillance
    • Political leaders informed. (TB curable and epidemic reversible)
    • Establishment of DOT by Bureau of Tuberculosis Control
      – DOT established in many chest clinics
      – Credible threat of detention for patients unwilling to adhere to Rx.
        Creation of locked TB ward
      – Preventive therapy and DOT established in commercial hotels (large numbers of HIV-infected persons housed, awaiting placement) – financial incentives
• Impacts of interventions
  – TB cases declined by 35.8% from 1992 peak to 1995
  – MDR-TB cases declined approx. 75% from 1992 to 1995
  – Sharp drop in US-born cases
• Foreign-born cases still increased in number and proportion of total cases
  – NYC – Immigrants and Refugees Unit to improve follow up and Tx of persons entering US with radiological TB evidence
Still to be done…

- Gaps in knowledge and applications to TB control
  - Lack of effective TB vaccine
  - Better anti-TB medications helpful
  - Epidemiology: Still lack of knowledge where and why most TB infections occur
    - Can’t ID smear-positive persons most likely infectious (much variability)
    - Poor understanding of host characteristics that determine infection or progression to disease
    - Transmission and virulence of different *M. tb* strains unknown
  - Uncertainty of proportion of patients with disease arising from recent infection
    - 10-20% vs. 30-40%? (In NYC, 50%)
    - Developing countries – adults already developed immunity, proportion of disease from recent transmission may be lower
    - For developing countries, TB be easier to control if proportion is higher (i.e. NYC).
      - Intensive emphasis on ID of cases and therapy completion
  - New epidemiologic investigations needed
XDR TB Response (Koenig)

- **Response**
  - WHO formed a global XDR TB task force
  - Recommendations
    - Better TB and HIV/AIDS control
    - Stricter management of drug-resistant TB
    - Better laboratory services
    - More extensive surveillance

- **Challenges**
  - Faster XDR detection needed
  - New treatment drugs
  - Involuntary Isolated patients
    - WHO recommends separating XDR TB patients
    - Patient unrest (escape from ward in Dec 2007)
    - Overcrowded hospitals