Tuberculosis Essentials: Overview of Disease Etiology, Diagnosis, Treatment

A Konstantinos
Queensland Tuberculosis Control centre
FIGURE 2.5  Estimated TB incidence rates, 2011

WHO: Global tuberculosis report 2012
Fig. 1

Natural history of tuberculosis in newly infected contacts

CONTACT WITH INFECTIOUS TUBERCULOSIS

No infection

10% of these people develop disease during their lifetime

- Bacterial load
- Aerosol generation
- Intensity and duration of exposure
- Ventilation

Infection

90% of these people never develop active disease

- Innate defences
- Cell-mediated immunity
- Malnutrition

5–8% develop disease within 5–7 years (majority within 1–2 years)

Small residual risk after 7 years due to immune suppression

Source: Australian Prescriber 33:12, 2010
Natural Determinants of TB

- Socioeconomic and environmental factors
  - crowding increases force of infection
  - poverty contributes to factors increasing host susceptibility
- Source factors
  - infectiousness
  - compliance / health seeking behaviour
- Host factors
  - closeness and extent of contact
  - Susceptibility to infection and disease
Discovery of anti-tuberculous drugs

• Selman Waksman / Albert Schatz
  – Streptomycin 1943

• Jörgen Lehmann
  – 4-aminosalicylic acid (PAS) 1944

• Gerhard Domagk
  – Conteben 1945 followed by isoniazid 1952
I have been horribly ill the last few weeks. I had a bit of a relapse, then they had another go with streptomycin, which previously did me a lot of good, at least temporarily. This time only one dose of it had ghastly results, as I had built up an allergy or something…

George Orwell
Drug resistance
Treatment failure
Relapse/reactivation

Streptomycin (1943) + PAS (1944) + isoniazid (1952)
short-term cure rates
resistance and relapses common when not used in combination
Initially SPH regimens were 18-24 months duration
Intermittent regimens effective if preceded by initial daily phase
Further Development of Modern (?) Standard Short (??) TB Regimen

Combination of isoniazid (H) + rifampicin (R) resulted in improved outcomes with fewer relapses after only (?) 9/12 treatment.

Addition of pyrazinamide to H + R regimens during initial 2/12 allowed further decrease in relapse rates and allowed overall regimen to be further shortened to 6/12.

6/12 regimen has been standard regimen for >30 years.
Fate of Bacillary cases of Pulmonary Tuberculosis under various treatment programs
(adapted from Grzybowski et Enarson. Bull IUAT 53:70-5, 1978)
THE EMERGENCE OF DRUG-RESISTANT TUBERCULOSIS IN NEW YORK CITY

THOMAS R. FRIEDEN, M.D., M.P.H., TIMOTHY STERLING, M.D., ANGEL PABLO-MENDOZA, M.D., M.P.H., JAMES O. KILBURN, Ph.D., GEORGE M. CAUFIELD, Sc.D., AND SAMUEL W. DOOLEY, M.D.

Abstract: Background. In the past decade the incidence of tuberculosis has increased nationwide and particularly in New York City. Method. We collected data on all cases of Mycobacterium tuberculosis in New York City from April 1991. Drug-susceptibility testing was performed at the Centers for Disease Control and Prevention. Results. Of the 5,150 patients with positive cultures, 45% (95% confidence interval) had isolates available for testing. Overall, 33% of these patients had isolates resistant to one or more anti-tuberculosis drugs. 25% had isolates resistant to both isoniazid and rifampin. Of the 299 patients who had received antituberculosis therapy, 44% had isolates resistant to one or more drugs and 30% had isolates resistant to both isoniazid and rifampin. Among the patients who had never been treated, the proportion with resistance to one or more drugs increased from 22% in 1989 to 25% in 1991 (P < 0.001). Conclusions. There has been a marked increase in drug-resistant tuberculosis in New York City. Previously treated patients, those infected with HIV, and injection-drug users are at increased risk for drug resistance. Measures to control and prevent drug-resistant tuberculosis are urgently needed.
WHO: Global tuberculosis report 2012
FIGURE 2.6  Estimated HIV prevalence in new TB cases, 2011

WHO: Global tuberculosis report 2012
New Determinants of TB

• Multi-drug resistant tuberculosis
  – resistance is result of failure to apply established principles of treatment
  – prevention requires close monitoring of use of evidence-based treatment regimens

• HIV infection
  – Risk of TB developing in HIV/TB co-infected host 5-10%/yr c.f. 5% life risk in normal host with TB infection (i.e., X 50-100 increased risk)

• Travel and mass displacement of people

• Inadequately established TB follow-up programmes

• Fragmentation of established TB follow-up programmes
The New England Journal of Medicine

THE EMERGENCE OF DRUG-RESISTANT TUBERCULOSIS IN NEW YORK CITY

THOMAS R. FRIEDEN, M.D., M.P.H., TIMOTHY STERLING, M.D., ARIEL PABLOS-MENDEZ, M.D., M.P.H., JAMES O. KILBURN, PH.D., GEORGE M. CAULFIELD, Sc.D., AND SAMUEL W. DOOLEY, M.D.

Abstract Background. In the past decade the incidence of tuberculosis has increased nationwide and especially in New York City, where there have been recent nosocomial outbreaks of multidrug-resistant tuberculosis.

Methods. We collected information on every patient with tuberculosis in New York City and laboratory results for Mycobacterium tuberculosis during April 1991. Drug-susceptibility testing was performed at the Centers for Disease Control and Prevention.

Results. Of the 518 patients with positive cultures, 468 (90 percent) had isolates available for testing. Overall, 33 percent of these patients had isolates resistant to one or more antituberculosis drugs, 25 percent had isolates resistant to both isoniazid and rifampin. Of the 359 patients who had received antimicrobial therapy, 44 percent had isolates resistant to one or more drugs and 30 percent had isolates resistant to both isoniazid and rifampin. Among the patients who had never been treated, the proportion with resistance to one or more drugs increased from 13 percent in 1980 to 26 percent in 1991 (P = 0.003). Patients who had never been treated and who were infected with the human immunodeficiency virus (HIV) or reported injection-drug use were more likely to have resistant isolates. Among patients with the acquired immunodeficiency syndrome (AIDS), those with resistant isolates were more likely to die during follow-up through January 1992 (90 percent vs. 47 percent, P = 0.02).

Conclusions. There has been a marked increase in drug-resistant tuberculosis in New York City. Previously treated patients, those infected with HIV, and injection-drug users are at increased risk for drug resistance. Measures to control and prevent drug-resistant tuberculosis are urgently needed.
Example from a NYC Public Hospital
(Brudney et Dobkin. ARRD 144:745-9, 1991)

Outcome of 178 patients discharged on TB treatment

19 (11%) adherent or died of AIDS (2)
159 (89%) nonadherent

148 (83%) lost within 3/12 of treatment inc. 99 (56%) with no follow-up after discharge

Outcome of 48 of the lost patients readmitted for TB treatment

7 died and 1 still on treatment at time of report
40 discharged

39 lost to follow-up (35 no follow-up and 4 <30 d)
New Determinants of TB

- Multi-drug resistant tuberculosis
  - resistance is result of failure to apply established principles of treatment
  - prevention requires close monitoring of use of evidence-based treatment regimens
- HIV infection
  - Risk of TB developing in HIV/TB co-infected host 5-10%/yr c.f. 5% life risk in normal host with TB infection (i.e., X 50-100 increased risk)
- Travel and mass displacement of people
- Inadequately established TB follow-up programmes
- Fragmentation of established TB follow-up programmes
Tuberculosis Notifications per 100,000 Population in Queensland:
1940 - 2010

Notifications per 100,000 population

Year


Notifications per 100,000 population
Figure 1: Tuberculosis (all) Rates in Queensland by Ethnic Group 2002 - 2011

Rate per 100,000 population

Year of Onset

Qld(all) NIAB Migrants (all)
Figure 9: Percentage of TB notifications in migrants in Queensland, 1965-2007

Percentage of TB notifications in migrants, 1965-2007
Symptoms of Tuberculosis

Cough >3 weeks

Fever/Sweating

Blood spitting

Loss of weight

Pain in chest

TEST SPUTUM x 3

Non-specific in low-prevalence settings
### Risk factors for tuberculosis in Australia

| Increased risk of tuberculosis infection (i.e. increased risk of exposure to infectious tuberculosis) | Migrants from high tuberculosis prevalence countries |
| | Members of Aboriginal and Torres Strait Islander communities with high incidence of tuberculosis |
| | Healthcare workers |
| | Household contacts (particularly children) of people at increased risk for tuberculosis |

| Increased risk of tuberculosis developing after infection† | HIV infection |
| | Silicosis |
| | Diabetes mellitus |
| | Chronic renal failure/haemodialysis |
| | Gastrectomy/jejunoileal bypass surgery |
| | Organ transplantation requiring immunosuppression |
| | Carcinoma (particularly head and neck carcinoma) |
| | Immunosuppressive therapies (corticosteroids, cytotoxic chemotherapy, tumour necrosis factor alpha inhibitors) |
| | Malnutrition and low body weight (≥10% less than ideal) |
| | Infancy |
| | Older age |

Source: Australian Prescriber 33:12, 2010
Factors associated with longer medical diagnostic delays – Qld experience

• Ward et al. IJTLD 5:1021-7, 2001
  – Increased age
  – Australian born
  – Time since migration

• Walpola et al. Unpublished data
  – Overseas students have longer medical diagnostic delays that other migrants
## Reasons for prolonged diagnostic delays (>3/12) S+PTB Qld 1985-98

(Ward, Siskind, Konstantinos IJTLD. 5:1021-7, 2001)

<table>
<thead>
<tr>
<th>Main reason for delay</th>
<th>Number</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated symptomatically (no TB investigations)</td>
<td>12</td>
<td>Cough attributed to asthma (2), bronchitis/respiratory infections (4), unspecified cause (6).</td>
</tr>
<tr>
<td>Misdiagnosis of CXR</td>
<td>8</td>
<td>CXR abnormalities attributed to cancer (1), pneumonia (1), old scarring (1), hydatid or fungal disease (1), unspecified cause (4).</td>
</tr>
<tr>
<td>Misdiagnosis of biopsy</td>
<td>3</td>
<td>Diagnoses were Crohn’s disease, sarcoidosis and Wegener’s granulomatosis</td>
</tr>
<tr>
<td>Failure to follow up result</td>
<td>1</td>
<td>Case initially presented with pneumonia and first sputum specimen lost. Second specimen not submitted until case represented with haemoptysis and paraplegia</td>
</tr>
<tr>
<td>Failure to pursue diagnosis</td>
<td>1</td>
<td>Abnormalities on CXR prompted consideration of TB but patient unable to provide sputum sample. TB diagnosed 3 months later when X-ray changes were evident and sputum was collected.</td>
</tr>
<tr>
<td>Initial appropriate investigations negative</td>
<td>5</td>
<td>Initial sputum smears or bronchcoscopy washings were negative.</td>
</tr>
<tr>
<td>Insufficient information</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>34</strong></td>
<td></td>
</tr>
</tbody>
</table>
Investigate for Pulmonary TB

• Sputum examination for TB
  – Smear, Nucleic acid amplification and culture
  – While smear lacks sensitivity, it detects infectious TB
  – Collect at presentation and on two subsequent mornings
• Induced sputum
  – If no adequate spontaneous sputum
• Bronchoscopy
  – Exclude alternative diagnoses
  – Always do sputum AFB smear first
If extrapulmonary tuberculosis

• Always exclude evidence of pulmonary TB
  – Pulmonary TB is the infectious form of TB
  – Chest X-ray
  – Sputum examination if indicated by symptoms of chest X-ray findings

NB Activity of TB cannot be accurately diagnosed on chest X-ray
Nucleic Acid Amplification tests and other molecular methods

• Rapid method
• For sputum, sensitivity less than that of culture but better than smear
• Very specific for TB
• Role of molecular technologies in early detection of MDR TB
• Importantly negative NAA result for TB does not equate to positive test for NTM – always consider pre-test probability
Tests for latent Tuberculosis

Have no role in the initial investigation for tuberculosis:

a) can delay appropriate investigations

b) negative tests do no exclude disease

c) positive tests supports probability of past exposure – not of disease
Remember

• Case-finding and treatment are the principle strategies for TB control
  – undiagnosed and untreated pulmonary TB is the source of transmission of TB
  – Infectious TB is easily diagnosed from sputum examination
  – need to always consider potential harm from delayed diagnosis (both individual human suffering and population risk)
Principles for Management of TB

• Isolation
  – Chemical
  – environmental

• Notification to public health authorities and early identification of high risk contacts

• Treat with evidence-based regimen in partnership with public health TB control unit
  – successful TB management requires close integration of clinical and public health principles
Principles of Tuberculosis Chemotherapy

• Prevent Emergence of Drug Resistance
  – Use appropriate combination of drugs to prevent natural selection of chemotherapy
  – Ensure compliance

• Eradicate *M. tuberculosis* from patient
  – bactericidal effect (intensive phase of treatment)
  – sterilizing effect – ensure duration of treatment sufficiently long to prevent failure and relapse

*Remember the first treatment course provides the best opportunity for cure*
Principles for Management of TB (cont)

• Ensure case holding with full compliance
  – Balance high index of suspicion with trust

• Need to objectively assess adherence
  – Establish patient responsibilities and health system responsibilities and ensure adherence to these
  – Objective assessments of adherence with drug regimen

• *These requirements can be met by effective partnership with public health TB unit*
Acknowledgements:
• QTBCC data management and clinical staff for help with data and for implementing the Qld case management approach to TB control
• All Queensland clinicians managing TB for willingly providing data and for having accepted partnership with QTBCC for the management of their patients

Thank you