Isolation and Quarantine: Evolving Evidence & Practice

US Public Health Perspective

Gisela Schecter, MD, MPH
University of San Francisco
California Department of Public Health

Definitions:

- Isolate: To put or keep (someone or something) in a place or situation that is separate from others.

- Isolation: The complete separation from others of a person suffering from contagious or infectious disease.

- Quarantine: Separation and restriction of movement of persons who, while not yet ill, have been infected with or exposed to an infectious agent and *may* become infectious.

Who is isolated?

- Patients suspected of having TB disease of the lung
  - What specimens should be collected?
  - How many specimens are needed?
  - What criteria need to be met to have TB “ruled out”?
- Patients with confirmed pulmonary TB
  - When can isolation be safely discontinued?
  - What about patients with MDR-TB?

Fundamentals of TB Infection Control (the Hierarchy)

- Administrative Controls
  - Effective policies for management of suspected or confirmed TB patients
  - TB screening program for HCWs
  - “cough” policy
- Environmental Controls
  - Airborne infection isolation rooms with negative pressure and frequent air exchanges
  - UVGI, HEPA filtration
- Personal respiratory protection
  - N95 respirators or PAPRs

Current Practice:

Controlling TB in the US: MMWR,2005

ATS, CDC, IDSA

- Traditionally, airborne infection isolation (AII) precautions can be discontinued when
  - Contagious TB is considered unlikely

AND

1) another diagnosis is made to explain symptoms

OR

2) 3 sputum specimens, separated by at least 8 hours, with one a first morning specimen, are AFB smear negative

- But:
  - 40 % of subsequently culture positive pulmonary TB cases are AFB smear negative
  - False positive AFB smears are relatively common in many parts of the US, due to NTMs

Can the use of NAATs improve our practice?

What is a NAAT?

- **NAAT: Nucleic Acid Amplification Test**
- Can be done on the direct clinical specimen; sputum, CSF, Lymph node aspirates, etc.
- More sensitive and more specific than the AFB smear
- Results available within hours to a few days
- CDC updated guidelines for NAATs in MMWR, Jan. 16, 2009:
  - "CDC recommends that NAA testing be performed on a least one respiratory specimen from each patient with signs and symptoms of pulmonary TB …" [if result will impact clinical or public health actions]

What is the added value of a NAAT?

- For AFB smear (–) patients:
  - Ability to confirm rapidly the presence of *Mtb* in 50-80% of AFB smear-negative , culture-positive specimens.
  - If both the AFB smear and the NAAT are negative, the likelihood of TB becomes very low
- For AFB smear (+) patients:
  - Greater positive predictive value (>95%) with AFB smear-positive specimens in settings in which NTM (non tuberculous mycobacteria) are common
  - If NAAT negative, in many instances can obviate the need for contact investigation

Current Practice:
CDC MMWR, October 18, 2013
Introduced Xpert/RIF assay

- Still recommends 3 sputum specimens be collected, separated by at least 8 hours, with one a first morning specimen
- Because NAA testing is significantly more sensitive and specific than microscopy, substitution of the Xpert/RIF assay (or another NAAT) increases the negative predictive value for *Mtb* if smear negative.
- Even if a sputum smear is positive, if all NAA tests are negative (after evaluation of all clinical information) AII precautions can be discontinued

Impact of NAATs on utilization of AIIRs and clinical care

- CDC sponsored retrospective multisite study* found using NAATS was associated with significant reductions in:
  - Use of AIIRs
  - Use of diagnostic procedures such as bronchoscopies and CTs
  - Initiation of CIs for smear positive, culture negative suspects
  - Time to diagnose of TB in smear positive cases
  - Duration of presumptive TB treatment for patients who did not have TB

*Marks SM, et.al. The health-system benefits and cost-effectiveness of using *Mtb* direct NAAT to diagnose TB disease in the US. Clin Infect Dis 2013

Do we need 3 sputum specimens to rule out TB?

- Prospective cohort study in North Carolina compared AIIR utilization using a one, two or three Xpert/RIF assay with a 3 AFB smear strategy.
- Median duration of AIIR was lower for all 3 Xpert arms
- The 3 smear, and the 2 and 3 Xpert strategies detected all culture positive cases, but the 1 Xpert strategy missed a case whose first AFB smear was negative.
- Is 2 NAATs the best strategy?

Limitations of NAATs

- 1) Inhibitors
  - Direct clinical specimens can contain inhibitors that prevent amplification
  - Results in false negative results
  - Xpert MTB/RIF includes a sample processing control (SPC) to monitor for presence of inhibitors
  - MTD procedure manual includes instructions on how to test for inhibitors
  - If an AFB smear (+) specimen is NAAT negative, make sure the lab checked for inhibitors, and repeat the NAAT on another specimen
- 2) Also, none of these tests will tell you if organisms are alive or dead
  - Should **NOT** be used to follow patients on treatment
  - Often NAAT will stay positive long after cultures are negative

Shifting Gears

Current Practice:
Controlling TB in the US: MMWR,2005
ATS, CDC, IDSA

- When during therapy is a patient with pulmonary TB no longer infectious?
  - No risk factors for MDR TB
  - Received standard multi-drug rx for 2-3 weeks. (For patients with AFB negative or only rarely positive, 5-7 days rx is sufficient.)
  - Complete adherence to treatment
  - Evidence of clinical improvement
  - Caveat: While in hospital or if returning to congregate setting, should *also* have 3 negative AFB sputum smears at least 8 hours apart (at least one an early morning specimen)

Current Practice:

Tb patient infectiousness and placement into high and lower risk settings

CTCA, CDPH

Category	Setting	Criteria
TB case or suspect on treatment for active TB -AFB smear positive -No risk factor for MDR-TB	High Risk	1) 3 consecutive respiratory specimens are AFB smear negative 2) At least 14 daily doses of treatment taken and tolerated 3) Clinical improvement
	Lower Risk	1) At least 14 daily doses of treatment taken and tolerated 2) Bacteriologic response to rx 3) Clinical improvement
TB case or suspect on treatment for TB -AFB smear negative X 3 -No risk factor for MDR-TB	High Risk	1) At least 5 daily doses of treatment taken and tolerated
	Lower Risk	1) At least one dose taken and tolerated

Current Practice:

Tb patient infectiousness and placement into high and lower risk settings

CTCA, CDPH

Category	Setting	Criteria
Known MDR-TB case	High Risk	1) 3 consecutive respiratory specimens are AFB smear negative 2) At least 14 daily doses of treatment for MDR-TB taken and tolerated 3) Clinical improvement 4) At least 2 consecutive negative sputum cultures
	Lower Risk	1) 3 consecutive respiratory specimens are AFB smear negative 2) At least 14 daily doses of treatment for MDR-TB taken and tolerated 3) Clinical improvement

Factors Influencing TB Transmission

- Transmission of TB is highly variable and depends on:
  - Source case factors
    - AFB smear status
    - Extent of Disease on CXR
    - Frequency and strength of cough
  - Pathogen factors
  - Environmental factors
    - Frequency and duration of exposure
    - Ventilation, U/V light, HEPA filtration
  - New host factors
    - Previous Mtb infection
    - Immune status (Very young/very old, HIV, etc.)

Factors affecting Infectiousness of TB to Household Contacts

Source-Case Variables	Tuberculin Reactors (%)
Radiographic Extent of Disease	
Minimal	16.1
Moderately advanced	28.3
Far advanced	61.5
Bacteriologic status	
Negative culture	14.3
Positive culture/negative smear	21.4
Positive smear	44.3
Mean 8-hour overnight cough count	
< 12	27.5
12-48	31.8
> 48	43.9

Loudon RG, Spohn SK. Cough frequency and infectivity in patients with pulmonary TB. Am Rev Resp Dis 1969; 99: 109-111.

Effects of Chemotherapy

- Rapid decline in sputum colony counts*
  - Reduction in sputum colony counts of almost 2 logs/ml after 2 days rx with INH/RIF/PZA/Strep
  - Further 1 log/ml drop in next 12 days
  - Thus, 99.9% decline in organisms/ml sputum in 2 weeks
- Decrease in cough frequency**
  - 65% reduction in cough frequency by 2 weeks on rx

*Jindani A, et al: The early bactericidal activity of drugs inpatients with pulmonary TB. Am Rev Resp Dis 121: 1980
**Loudon RG, et al: Cough frequency and infectivity in patients with pulmonary TB. Am Rev Resp Dis 99: 1969

Effects of Chemotherapy:
Guinea Pigs

Effects of Chemotherapy

Relative infectiousness of treated and untreated patients*

TB Patients	Guinea pigs infected (n)	Relative risk of infection Adjusted for time on ward
Drug-susceptible		
Untreated (n=61)	29	100
Treated (n=29)	1	2
Drug-resistant		
Untreated (n=6)	14	28
Treated (n=11)	6	5

*Riley RL, et al: Infectiousness of air from a tuberculosis ward.... Am Rev Respir Dis 1962; 85: 511-525

Effects of Chemotherapy: What about MDR TB?

DST of isolates from patients in 5 human-to-guinea pig transmission experiments*

Experiment	Isolates with full DST (# of subjects)	XDR-TB isolates	Proportion guinea pigs infected, %
Pilot	11(26)	3	74
Experiment 1	10 (24)	5	10
Experiment 2	11 (15)	2	54
Experiment 3	21 (27)	0	1
Experiment 4	10 (17)	2	27

*Dharmadhikari AS, et al. Rapid impact of effective treatment on transmission of multidrug-resistant TB. Int J Tuberc Lung Dis 2014; 18(9): 1019-1025

Variability of Infectiousness

- Even if all these factors are taken into consideration, there is still significant variability in transmission rates between patients.
  - Epi studies suggest that only 1/3 of AFB + patients infect their contacts
  - An estimated 17% of active TB cases can be attributed to smear negative source cases
  - In one of Riley's early studies only 8 of 61 patients with pulmonary TB transmitted TB to guinea pigs.
  - Adolescents and young adults are typically more infectious than the elderly
  - Low viscosity of sputum contributes to increased transmission

Can cough aerosols* better predict transmission?

- TB must be aerosolized to transmit
- Only about 1/3 of smear positive patients will generate aerosols. Positive aerosols associated with
  - Higher Karnofsky scores
  - Higher AFB smear grade
  - Shorter time to positive culture
  - Stronger cough
  - Thinner sputum (mucosalivary vs purulent)
  - Fewer days on treatment

*Fennelly KP, et al. Variability of infectious aerosols produced during coughing by patients with pulmonary TB. Am J Respir Crit Care Med 2012;186: 450-457.

Can cough aerosols better predict transmission?

- Fennelly's group* then looked at prediction of new infections
  - Contacts of patients with high aerosols (>10 CFU) more likely to have a new infection c/w low aerosols or negative cases
    - High CFU count = 69%
    - Low CFU count = 25%
    - Negative CFU count = 30%

*Jones-Lopez EC, et al. Cough aerosols of *Mtb* predict new infection: a household contact study. Am J Respir Crit Care Med 2013; 187: 1007-15.

The Way Forward: Summary

- TB transmission is highly variable
- Use of NAATs can improve our utilization of TB isolation resources
- Effective chemotherapy of active TB is the most effective way to prevent ongoing transmission
- Patients with MDR-TB on effective treatment, probably become non contagious more rapidly than previously thought
- Clinical acumen and judgment are still needed when determining an individual patient's infectiousness.