

Chest X-rays in Tuberculosis Trials

Conor Tweed

Andrew Nunn

MRC CTU at UCL

INTERTB 17th November 2017

MRC Streptomycin Trial (1948)

- Medical Research Council (1948). Streptomycin treatment of pulmonary tuberculosis: a Medical Research Council investigation. *BMJ* 2:769-782.

MRC Streptomycin Trial (1948)

- Medical Research Council (1948). Streptomycin treatment of pulmonary tuberculosis: a Medical Research Council investigation. *BMJ* 2:769-782.

BMRC Studies Chest X-ray Criteria

- Extent of disease:
 - Total area with evidence of disease
 - Scale of 0 – 6 representing number of zones affected
- Cavitation:
 - No cavities
 - 2cm or less in diameter
 - 2 – 4cm in diameter
 - 4cm or more in diameter
- Change in disease assessed in terms of changes in extent and cavitation

BMRC Studies

- Stratified by presence of cavitation at one year when analysing for risk of relapse in 1957-1961¹
- Used as a tool for diagnosing, assessing treatment response², and detecting relapse
- CXR changes to identify relapse in short course (2-3 month) treatments with negative smear³

¹ Devadatta S et al. Bull World Health Organ 1961

² British Medical Research Council. Tubercle 1970

³ Medical Research Council. Lancet 1979

Chest X-rays in TB



- Pros:
 - Equipment is cheap and training relatively simple
 - Established role in TB diagnosis
 - Ability to detect active disease in asymptomatic patients with negative microbiology
- Cons:
 - No role in latent disease and may miss subtle/early TB
 - Presentation of TB is variable, and can be mimicked by other conditions
 - Inter-observer variability in reporting

Ralph Scoring System

- Numerical score designed to grade TB severity and predict treatment response¹
- Score composed of the estimated proportion of lung affected (out of 100) with 40 points added if one or more cavities present
- Significant association with smear at baseline and 2 months, and score decreased during treatment

¹ Ralph et al. Thorax 2010

Ralph Scoring System

- Simple score to calculate, suitable for trials and clinical practice
- Good indication of bacterial load at baseline
- However:
 - High inter-observer variability
 - Limited conclusions relating to treatment outcome (2 month smear as end-point)
 - Unclear applications in MDR-TB and HIV positive

CSSR Scoring System

- Aimed to produce a reading system for community-based research with provision for quantitation of findings¹
- Assesses films based on large/small opacities, cavities, pleural abnormalities, central abnormalities, and lymphadenopathy
- Pinto et al² proposed a score for the diagnosis of TB based on upper lobe opacities, cavitation, pleural effusion, and adenopathy

¹ Den Boon et al. Int J Tuberc Lung Dis 2005

² Pinto et al. PLOS One 2013

CSSR Scoring System

- Negative predictive value of >91%, even in smear negative patients
- Acts as a supplement to smear/culture and clinical history/examination
- Drawbacks:
 - Confirmatory testing would be more useful
 - Requires more skilled interpretation compared to Ralph score
 - Uncertain application in assessing severity of disease and treatment monitoring

Chest X-rays in REMoxTB¹

	Number unfavourable / Number assessable (%)		
	Control Arm (2HRZE/4HR)	Isoniazid Arm (2MHRZ/2MHR)	Ethambutol Arm (2EMRZ/2MR)
Cavitation Present	34 / 368 (9%)	60 / 357 (17%)	83 / 367 (23%)
Cavitation Absent	6 / 96 (6%)	6 / 104 (6%)	13 / 108 (12%)

- Proportionately more unfavourable treatment outcomes in those with cavitation on experimental arms

¹ Gillespie et al. N Eng J Med 2014

Chest X-rays in OFLOTUB¹

		Number unfavourable / Number assessable (%)		
		Control Arm (2HRZE/4HR)	Gatifloxacin Arm (2HRZGat/2HRGat)	P value for interaction
Cavitation				
	Present	50 / 332 (15.1%)	80 / 360 (22.8%)	0.04
	Absent	64 / 324 (19.8%)	63 / 333 (18.9%)	
Disease Zone Score				
	0 - 1	5 / 46 (10.9%)	8 / 59 (13.6%)	0.47
	2 - 3	49 / 324 (15.1%)	53 / 327 (16.2%)	
	4 - 6	59 / 282 (20.9%)	84 / 304 (27.6%)	

¹ Merle et al. N Eng J Med 2014

Chest X-rays in RIFAQUIN¹

		Number unfavourable / Number assessable (%)			
		Control Arm (2HRZE/4HR)	4 Month Arm (2EMRZ/2M ₂ P ₂)	6 Month Arm (2EMRZ/4M ₁ P ₁)	P value for trend
Cavitation					
	Present	19 / 116 (16%)	27 / 117 (23%)	18 / 123 (15%)	0.65
	Absent	6 / 55 (11%)	21 / 61 (34%)	10 / 73 (14%)	
Disease Zone Score					
	0 - 1	5 / 54 (9%)	13 / 52 (25%)	8 / 72 (11%)	0.02
	2 - 3	14 / 92 (15%)	30 / 103 (29%)	11 / 90 (12%)	
	4 - 6	6 / 25 (24%)	5 / 23 (22%)	9 / 34 (26%)	

¹ Jindani et al. N Eng J Med 2014

Chest X-rays in Recent Phase III Trials

- Cavitation associated with higher proportions of unfavourable outcomes on experimental arms
- Similar proportions of unfavourable outcomes in standard therapy and experimental arms in absence of cavities
- Extent of disease variably associated with unfavourable outcomes

Current Needs and Future Directions

- Diagnosis:
 - “Rule in” features diagnostic for TB vs other lung pathology
 - Using more advanced imaging techniques and correlate with CXR¹
 - Automated reading systems based on machine learning/neural networks²
 - Combining a clinical scoring system with robust X-ray score to reach diagnosis with minimal training

¹ Esmail et al. Nat Med 2016

² Maduskar et al. Int J Tuberc Lung Dis 2013

Current Needs and Future Directions

- Treatment monitoring and prediction of relapse:
 - Identifying patients who require additional monitoring with longer/shorter therapy
 - Previous attempt to shorten treatment in patients with CXR improvement demonstrated rate ratio 3.4 for relapse at 1 year¹
 - Unlikely to be single indicator but combined with microbiology, clinical picture, and biomarkers

¹ Johnson et al. Am J Respir Crit Care Med 2009

Conclusion

- CXR remains a simple and cheap component of TB diagnosis in widespread use
- Indicates severity of disease and is related to treatment outcome to some extent
- Blunt tool with potential for high levels of inter-reader variability
- Despite increased interest in more advanced imaging techniques for TB, CXR still potentially has a valuable role to play in diagnostics and treatment monitoring

Thank you

c.tweed@ucl.ac.uk