Does TB culture impact on clinical decision-making?

Pamela Hepple
Medecins Sans Frontieres UK
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Pamela.HEPPLE@london.msf.org

Why culture?

- Löwenstein-Jensen medium was developed in 1932, with liquid media and thin layer agar subsequently allowing detection of growth to be speeded up
- While culture has become the gold standard for tuberculosis diagnosis globally, most high burden countries rely on microscopy for diagnosis (sensitivity <65% c.f. culture)
- In 2009, WHO called for universal access to TB culture by 2015
- The STOP TB partnership set up the Global Laboratory Initiative (GLI) to help facilitate this:

GLI - Mission and strategic priorities

To serve as a platform of coordination and communication, providing the required infrastructure, focused on TB laboratory strengthening, in the areas of:

- Global policy guidance on appropriate laboratory technology and best practices
- Laboratory capacity development
- Interface with other laboratory networks to ensure appropriate integration
- Standardized laboratory quality assurance
- Coordination of technical assistance
- Effective knowledge sharing
- Advocacy and resource mobilization

But don't we have those great molecular tests now?

- Hain Genotype MTBDRplus and Xpert MTB/RIF, in particular, have been endorsed by WHO for rapid detection of Rifampicin resistance (Hain), and resistance plus diagnosis (Xpert)
- However, in the 2008 recommendation for Hain, it was stated that culture was still required for smear-negative diagnosis and drug sensitivity testing for 2nd line drugs, especially where XDR TB is suspected. The 2011 recommendation for Xpert stated culture is still required for treatment monitoring and DST for drugs other than Rifampicin
- The extensive roll-out of Xpert implies that even greater culture capacity will be required for follow-up of people on treatment, as well as investigation of resistance to 2nd line drugs

So what happens when culture is implemented?

- Surely lots more people get accurate diagnoses and many lives are saved?

What impact does culture have in clinical decision-making?

- 4 papers investigate this, from:
  - India (1)*
  - Sudan (-)
  - Taiwan (2 - China)
  - Brazil (14)

- *TB high burden countries global ranking by estimated cases

Stall *et al*, 2011 - Does solid culture for tuberculosis influence clinical decision making in India?

- Setting: 3y referral hospital, South India
- Objective: to investigate the impact of solid culture on LJ on clinical decision-making
- Design: Retrospective review of 150 culture-positive and 150 culture-negative TB suspects. Treatment decisions were analysed at presentation, after availability of culture results, and after availability of DST results

Results

- 124/150 of culture-positive and 35/150 of culture-negative patients started TB treatment prior to culture results being available
- Only 101/300 (33.7%) of patients returned for culture results
- 2/300 (1.3%) started treatment based on positive culture
- No culture-negative patients discontinued treatment

- DST performed on 119/150 (79.3%) of positive samples:
  - 89/119 (74.8%) fully susceptible
  - 30/119 (25.2%) any resistance
  - 8/119 (6.7%) MDR
  - 1/119 (0.84%) XDR
- 28/119 (23.5%) returned for their DST results
- Based on DST, treatment was modified for 4 (3.4%) patients

- => only 2/150 culture-positive patients, and no culture-negative patients, had treatment modified based on culture results, and only 4/119 culture-positive patients had treatment modified based on DST results
- Mean TAT for positive culture detection = 55.4 days (SD+/- 25.9)
- Mean TAT for DST result = 109.2 days (SD +/- 29.7)

- 26/150 patients were not treated at presentation, and 35/150 culture-negative patients were 'treated unnecessarily' (debatable?). 2/8 MDR patients were not treated at presentation, therefore culture results did provide valuable information – but too late, or not considered by the clinicians when available (e.g. for MDR treatment modification).
- However – patient reassessment delays were also significant (appointments were on average 47 days after culture-positive results were available, and 50 days after culture-negative results were out)
- Conclusion: a rapid test is required, and patient-relevant outcomes should be considered when guiding diagnostic choice

Hepple *et al*, 2011 - Implementation of liquid culture for tuberculosis diagnosis in a remote setting: lessons learned

- Setting: Southern Sudan/Kenya border (samples were collected in villages in Sudan and flown to Lokichoggio, Kenya for culture)
- Objective: analysis of impact of liquid culture on clinical decisions
- Design: retrospective analysis of lab data from TB diagnostic and treatment failure suspects

Results

Table Culture results by type of mycobacteria

	Diagnostic patients (n = 73)		Treatment patients (n = 27)		
	Smear-negative (n = 70) n (%)	Smear-positive (n = 3) n (%)	Smear-negative (n = 20) n (%)	Smear-positive (n = 7) n (%)	EPTB patients (n = 20) n (%)
M. tuberculosis complex	8 (11)	2 (67)	0	1 (14)*	3 (15)
Other identified mycobacteria	7 (10)†	1 (33)‡	5 (25)§	2 (29)¶	0
Other unknown mycobacteria	8 (11)	0	4 (20)	0	3 (15)
Culture-negative	47 (67)	0	11 (55)	4 (57)	14 (70)

*Plus *M. fortuitum*.
†*M. intracellulare* (n = 1), *M. asiaticum* (n = 1), *M. margaritense* (n = 1), *M. avium* complex (n = 2) and *M. fortuitum* complex (n = 2).
‡*M. fortuitum*.
§*M. fortuitum* complex (n = 4), *M. avium* complex (n = 1). ¶*M. intracellulare* (n = 1), *M. fortuitum* complex (n = 1).
EPTB = extra-pulmonary tuberculosis.

- The high proportion of NTM was mainly in SM- samples and probably due to environmental contamination at the patient level, as opposed to lab level, due to the variety of species recovered (50% of which couldn't be identified by genotyping)
- Steps were taken to control this suspected contamination, and lab contamination rates reduced from 25% to <10%, but NTM rates did not decrease
- Clinicians found it very difficult to interpret these results, and ended up ignoring them

- TAT to results was 4-6 weeks – too long for clinicians to suspend decision-making, particularly as patient populations tend to be nomadic and are easily lost to follow-up
- Long TAT was due to positive samples being sent to Borstel NRL (Germany) for speciation (prior to SD Bioline, BD etc speciation tests were available, and Capilia was difficult to source)
- Therefore, the (extremely expensive: each strain shipment cost USD500!) culture programme was suspended in 2009

- N.B.: the ATS recommendation for dealing with NTM isolation (the same species must be recovered at least twice to be considered clinically significant) was not practicable in this setting due to the high rates of loss to follow up
- (We continue to send some samples to ITM for culture and DST, and NTM and contamination rate issues occur even there…)

PCR

- Some SM+ sputum samples (approx. 20) were sent to Borstel for direct LPA analysis
- All gave viable results – all were TB
- This implies that smear-positives probably contained TB which may have been overgrown by faster-growing NTM
- Also implies that PCR is a better platform for heavily-contaminated samples

- Conclusions:
  - Liquid culture was not useful for diagnosis or treatment monitoring in this setting
  - Appropriate guidelines are required to help with NTM interpretation in resource-limited settings

Chiang *et al*, 2008 - Factors associated with a clinician's decision to stop anti-tuberculosis treatment before completion

- Setting: Taipei City, Taiwan
- Objective: to investigate the diagnosis of pulmonary tuberculosis and factors associated with a clinician's decision to stop anti-TB treatment before completion
- Design: Retrospective review of medical charts of all people treated for TB in Taipei

Results

- 139/1126 (12.3%) of patients were treated based on a positive culture – the others were treated based on x-ray, smear or 'other findings'
- Patients whose diagnosis was based on CXR (aOR 2.2, 95% CI 1.1-4.4) and other findings (aOR 3.2, 95% CI 1.6-6.7) were significantly more likely to have their diagnosis changed than those whose diagnosis was based on culture
- Therefore, culture results, when used, were respected in this setting

Dowdy *et al*, 2008: Impact and cost-effectiveness of culture for diagnosis of tuberculosis in HIV-infected Brazilian adults

- Setting: urban TB culture programme for HIV-infected patients, Brazil
- Objective: to estimate the impact and cost-effectiveness of mycobacterial culture for the diagnosis of TB in an urban setting in Latin America
- Design: analysis of patient records and costs associated with TB culture

Results

- 33/217 (15%) had culture-confirmed active TB
- 23/33 (70%) of these were smear-negative
- Of 23 smear-negative:
  - 6 (26%)began TB therapy before culture results were available
  - 11 (48%) began therapy after culture results were available
  - 6 (26%) did not begin treatment within 180 days of presentation

The maths bit…

- Cost per negative culture: USD17.52 (solid) or USD23.50 (liquid)
- Per 1,000 suspects, c.f. smear alone, solid culture would avert an estimated **8** TB deaths (95% SI: 4, 15) and 37 DALYs (95% SI: 13, 76), at a cost of **USD36** (95% SI: USD25, USD50) per TB suspect, or **USD962** (95% SI: USD469, USD2642) per DALY averted
- Replacing solid media with automated liquid culture would avert **1** further death (95% SI: 1,4) and **8** DALYs (95% SI: 4, 23) at **USD 2752** per DALY (95% SI: USD 680, dominated)

- Conclusion: TB culture is potentially effective and cost-effective for HIV-positive patients in resource-limited settings.
- Reliable transmission of results is essential.

By the way

- Tariq & Tariq, 2004: Empirical treatment for tuberculosis: survey of cases treated over 2 years in a London area (J Pak Med Assoc)
- Empirical treatment (without biological confirmation) for TB was far more likely to be given to Asian and African patients c.f. West Europeans
- (Also in Ireland…)

Overall conclusions

- Implementation of culture alone isn't enough to have a positive impact on TB treatment
- Clinician education in the importance of culture results with regard to treatment implementation and management is important
- Patient education on the importance of returning for test results is also crucial
- Establishment of efficient administration systems whereby TAT to ***results in front of the patient*** is minimised must be implemented (not just available in the lab or in the patient's file)
- But, to give clinicians their due, rapid tests are also necessary to aid the challenging clinical decisions that must be taken when treating TB

Thanks