

# Post TB Lung Disease (PTLD)

Douglas Hornick, MD Pulmonologist with an Infectious Attitude

# **Objectives**

- Provide overview of Post-TB lung disease (PTLD)
- Review & discuss 6 standards proposed for early identification, severity assessment, management by pulmonary rehabilitation (PR), while also addressing public health implications
- Review Research Priorities

# Consensus-Based Common Sense Recommendations

Migliori et al. Clinical standards for the assessment, management and rehabilitation of post-TB lung disease.

Int J Tuberc Lung Dis 25(10):797-813 2021

# Post TB Lung Disease (PTLD)

- Definition: Chronic respiratory abnormality w/wo symptoms wholly or partly attributable to prior pulmonary TB
- ~30 million  $\approx$  20% of treated pulmonary TB past 5 yrs
- Spectrum of clinical lung patterns (Table/Radiographs)
- Other problems
  - Secondary infection (Abscess, NTM, *P. aeruginosa*, Aspergillus)
  - Cardiovascular disease d/t prolonged lung infection/inflammation
  - Risk of TB relapse or reinfection
- Contribute to cough, weakness, dyspnea,  $\downarrow$  QOL,  $\uparrow$  Death
- Objective measures: Pulmonary function testing (obstruction, restriction or mixed), cardiopulmonary ex test

Migliori et al. Int J Tuberc Lung Dis 25(10):797-813 2021

# **PTLD Clinical Patterns**

Compartment	Clinical patterns	Suggested definition
Airways	Tuberculosis-associated obstructive lung disease	Airway obstruction (FEV1/FVC ratio <0.7 OR <lln) airway="" disease<="" primarily="" related="" small="" td="" thought="" to=""></lln)>
	Bronchiectasis	CT definition – evidence of airway dilatation > diameter of adjacent vessel, or non-tapering, or CXR definition – evidence of ring shadows and tramlines
Parenchyma	Cavitation	A gas-filled space either within an area of pulmonary consolidation or surrounded by a thin wall
	Parenchymal destruction	Extensive destruction of lung tissue, with a gas-filled space/collapsed parenchyma occupying the volume of $\ge 1$ lobe
	Fibrotic change	Areas of parenchymal scarring with associated volume loss
	Aspergillus-related lung disease	Evidence of aspergilloma on imaging or chronic pulmonary aspergillosis on imaging and blood testing
Pleural	Chronic pleural disease	Evidence of pleural thickening on CXR or CT imaging
Pulmonary vascular	Pulmonary hypertension	Elevated pulmonary artery pressures, as estimated using Doppler echocardiography or measured at right heart catheterisation

#### PTLD Bronchiectasis Evaluated best by Chest CT

#### **Localized Bronchiectasis**



#### **RUL & RLL**

#### LUL & Lingula

#### Ę

## PTLD: Atelectatic Bronchiectasis & Volume Loss

#### **Atelectatic Bronchiectasis**



LUL Atelectatic Bronchiectasis; Residual nodularity superior seg LLL

#### Atelectatic Bronchiectasis; Comp Hyperinflation R



### **PTLD: Residual Cavitation & Volume Loss**



#### RUL Residual Cavitation & Volume Loss

#### L lung destroyed & Volume Loss

#### **Adolescent post TB Chest X-ray**



Children get PTLD...Less known about outcomes, lung function, etc

# Post TB Lung Disease (PTLD)

- Definition: Chronic respiratory abnormality w/wo symptoms wholly or partly attributable to prior pulmonary TB
- ~30 million  $\approx$  20% of treated pulmonary TB past 5 yrs
- Spectrum of clinical lung patterns (Table)
- Other problems
  - Secondary infection (ie, Abscess, NTM, P. aeruginosa, Aspergillus)
  - Cardiovascular disease d/t prolonged lung infection/inflammation
  - Risk of TB relapse or reinfection
- Contribute to cough, weakness, dyspnea,  $\downarrow$  QOL,  $\uparrow$  Death
- Objective measures: Pulmonary function testing (obstruction, restriction or mixed), cardiopulmonary ex test

Migliori et al. Int J Tuberc Lung Dis 25(10):797-813 2021

# **Delphi Process...**

- 67 world experts invited, 62 participated
  - 34 clinicians, 18 public health, 6 PR, 3 Peds, 3 Pulm Physiology, 2 Methodologists, 1 Psychologist
- Developed 6 Standards
  - 5 clinical
    - 1 Evaluation recommendations
    - 2-4 Pulmonary Rehabilitation Indications, Feasibility, Impact evaluation
    - 5 Post Rehab Plans
  - Public Health

### Standard 1: Assess TB patient for PTLD

- Assess indications for Pulmonary Rehab (PR): H&P (vax hx, comorbid, RF, occ exp), CXR, PFT, 6MWT, Symptom & QOL
- Chest CT (cost/rad exposure) adds better resolution for bronchiectasis, cavity extent, signs of relapse, new dx (ie, NTM)
- PFTs (Spiro, Vol, DLCO) post Rx as "new baseline"
- 6MWT correlates with severity of chronic resp disease, few resources required
- Select pts: CV risk assessment (BNP, CRP, lipids)
- Symptom/QOL assessment
- Specific Considerations for Peds
  - Lack of data about long-lasting consequences of Pulm TB
  - ~50% clinical dx TB (no microbiologic confirmation/paucibacillary TB)
  - CXR primary tool...Chest CT problematic
  - Spirometry children >4-6 yo; Oscillometry/Multiple Breath Washout <4, data on lung function impairment non-existent</li>
  - 6MWT for >4 yo (ref ranges for Caucasian)
  - EQ-5D-y and/or Toddler and Infant (TANDI) QOL questionnaire (US)

### Standard 2: Identify Pts for Pulm Rehab (PR)

#### **Evaluation includes**

- Hx/PX,
  - RF for severity: Delay in Dx &/or Rx, Inappropriate Rx, extended Rx and /or MDR/XDR TB
- Radiographs that point to PTLD,
- Abnormal PFTs (obs/res), hypoxemia, ↓ 6MWT
- Abnl Symptom/QOL scores
- Effective PR (American Thoracic Society [ATS] Workshop 2021)
- Comprehensive multi-disciplinary package
- Exercise...also nutrition, respiratory & selfmanagement skills, education, & psychosocial support

# **PR--ATS Workshop Report**

- Benefits of PR for COPD: Level 1 supportive evidence
  - Improves exercise capacity & enhances health-related QOL
  - Reduces dyspnea & hospital admissions
  - Evidence accruing that these benefits extend to other ds: ILD, bronchiectasis & pulmonary hypertension
- PR reduces hospital admits, improves survival in COPD subset suffering severe exacerbations
- Despite benefits, PR grossly underused worldwide...
  - US & Canada < 5% eligible pts undertake PR
  - Striving to make PR more widely accessible w/o ↓ benefits

Holland et al. *Ann ATS* 18(5) 2021



#### Standard 3: Tailoring PR to Patient Needs & Resources

- Must include: BL & post PR outcome measures Structured, supervised exercise program Education/Behavioral programs Provide recs for home-based exercises
- Paucity data to guide low resource areas selecting essential parts to avoid undermining beneficial effect
- Unspecified adaptations for children/adolescents
- Comprehensive details found in Table 3

## **Standard 4: Evaluate Effectiveness of PR**

		Type of measure	
	Outcomes	Essential and conditional examinations/investigations	Adaption to special setting and situations
Functional	Lung function	<ul> <li>Spirometry (FEV<sub>1</sub>, FVC, FEV<sub>1</sub>/FVC)</li> <li>Plethysmography</li> </ul>	• Spirometry (FEV <sub>1</sub> , FVC, FEV <sub>1</sub> /FVC)
	Gas transfer	<ul> <li>PaO<sub>2</sub>,</li> <li>PaCO<sub>2</sub></li> <li>Pulse oximetry (SpO<sub>2</sub> % desaturation)</li> </ul>	<ul> <li>Pulse oximetry (SpO<sub>2</sub>, % desaturation)</li> </ul>
	Exercise capacity	<ul> <li>DLCO, K</li> <li>6MWT</li> <li>6MWT</li></ul>	& data for PTLD 5-45 m to that reported for COPD
TB-specific	Health-related quality of life	<ul> <li>EUROHIS-QOL 8</li> <li>SGRQ</li> <li>WHOQOL-BREF</li> </ul>	<ul> <li>EUROHIS-QOL 8</li> <li>SGRQ</li> <li>WHOQOL-BREF</li> </ul>
	Self-reported symptoms	<ul> <li>Paediatric: EQ-5D-Y and TANDI</li> <li>mMRC</li> <li>VAS</li> <li>Modified Borg</li> </ul>	<ul> <li>paediatric: EQ-5D-Y and TANDI</li> <li>mMRC</li> <li>VAS</li> <li>Modified Borg</li> </ul>
Generic	Acute infectious exacerbations (e.g., in bronchiectasis) requiring antibiotic and/or steroid treatment	Number of episodes	Number of episodes
	Hospitalisation Mortality (see Standard 6)	Number of episodes/hospital days Number of deaths	Number of episodes/hospital days Number of deaths

#### Throughout admonishments maintain high index of suspicion for TB relapses

#### Standard 5: Education & Counselling

Each Post PR pt → Counseling/health education Implement plan to maintain benefits Tailored & specific to individual needs/resources

Summary of components suggested for counselling & education sessions:

Components:

- Structured and comprehensive educational programmes are an integral and essential component of the management of PTLD and pulmonary rehabilitation
- Educational programmes should be age-specific, gendersensitive, delivered in the local language and extended to families/households
- Education should be delivered by professionals who are competent in the relevant subject areas and trained to deliver educational sessions
- Educational materials and technological support used to deliver them needs to be evaluated in the setting-specific context

Recommended topics:

- Basic principles of TB: epidemiology, clinical aspects and transmission (reinforcing what is ideally provided at diagnosis)
- Importance of treatment (and treatment adherence/retention in care) to stop transmission, protect contacts and prevent relapses
- Simple concepts of infection control and safety procedures
- Advantages/importance of smoking cessation and risk of comorbidities (e.g., HIV co-infection, diabetes, etc.) in household/families
- Importance of physical activity and exercise to improve quality of life
- Maintaining results achieved with pulmonary rehabilitation (follow-up plan)
- Ensuring adequate nutrition
- Importance of adhering to medical prescriptions in terms of management of comorbidities and vaccinations
- Recognising deterioration of clinical conditions and what actions to undertake to prevent relapse
- Achieving an optimal healthy life style

#### **Standard 6: Public Health Aspects**

- PR implementation fits w/ revised WHO recs to f/u 6-12 mos post cure
  - Monitor for relapse & reinfection
  - Achieve "sustained cure"
- Update TB register with data from PR outcomes
- Advocate on behalf of PTLD pt to assure access to social support schemes based on local resources

# **Research Priorities**

	Research priority	Type of studies
1)	To describe the frequency and severity of PTLD in different populations and subgroups of TB patients over time since the completion of TB treatment, including in children and adolescents	Cross-sectional studies, cohort studies
2)	To establish risk factors for severe PTLD and associated poor health outcomes, including elevated mortality	Cohort studies (case-control studies)
3)	To quantify the health and economic impact of PTLD at the individual and population level, including the impact of managing PTLD on health systems	Health economic/mathematical modelling studies
4)	To identify feasible, accurate and cost-effective tools to evaluate patients at the end of TB treatment for their risk of PTLD and subsequent poor health outcomes (Standard 1)	Diagnostic accuracy studies, diagnostic randomised-controlled trials
5)	To develop optimal approaches and algorithms to diagnose and manage PTLD, and to discriminate between PTLD and recurrent TB (Standards 1, 2)	Diagnostic accuracy studies, diagnostic randomised-controlled trials
6)	To identify effective and cost-effective strategies to prevent PTLD during anti-TB treatment, including, for example, adjuvant therapies and interventions to reduce concomitant risk factors for poor lung health outcomes (e.g., smoking cessation programmes)	Randomised-controlled trials
7)	To identify effective and cost-effective strategies to deliver pulmonary rehabilitation in specific sub-groups (using standard measures of minimum clinically important difference), including individual patient follow-up in different settings and populations (Standards 2–5)	Randomised-controlled trials
8)	To investigate the role of patient education programmes in improving long-term health outcomes post-TB (Standard 5)	Randomised-controlled trials
9)	To investigate the role of social protection and support programmes in improving health outcomes and quality of life among former TB patients (Standard 6)	Randomised-controlled trials
10)	To identify a set of standard indicators for the surveillance of PTLD that are feasible to implement within national TB programmes (Standard 6)	Operational research studies

#### PTLD Severity Varies Directly with PMN 1<sup>st</sup> Month

#### N= 154, Retrospective analysis

Evaluated PMN RALPH Score (Radiograph Severity)



- PMNs higher in those w persistent cavity, pleural effusion, pleural thickened & volume loss
- Retrospective...lacks functional correlates (ie, PFT, 6MWT)

Jones TPW et al. Chest Dec 2021

#### Concurrent Anti-inflammatory Adjunctive TB Rx to Reduce PTLD

- Spirometry benefit a/w co-administration Everolimus (mTOR inhibitor) & CC-11050 (type 4 PDE inhibitor) concurrently taken day 1-112 of TB treatment
  - Randomized, prospective, open label cp 4 arms vs placebo, N ~40 each arm
  - Selected severe based on CXR & Ct below 20
  - Auranofin (anti-inflammatory gold salt) & Vit D insignificant effect
- Small pilot study showed benefit with Doxycycline (MMP inhibitor) co-administration day 1-14
  - Randomized DB, PC, N = 30
  - Accelerated resolution of Inflammatory RNA signatures, ↓MMP, & ↓ lung cavity volume

Wallis et al. *Lancet Resp Med* 9:897 2021 Miow et al *JCI* 131(15) 2021

# Conclusion

- PTLD significant problem, substantial negative impact
- Seven consensus based standards reviewed
  - Highly recommends getting PR to impaired patients
  - Identifies areas where more work needed
  - Does not include much for children
  - Includes public health and research priorities
- Promising research sampled