Pediatric Tuberculosis

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Children are not small adults!
Objectives

At the end of this session, participants will be able to:

- Define the clinical and radiographic manifestations of tuberculosis in the pediatric population
- Discuss the appropriate work up for pediatric patients with suspected tuberculosis
- List therapeutic modalities for children with tuberculosis
Case 1 – History

• This is a 5 year old female brought to your clinic for evaluation of positive TST (13mm), placed for contact investigation.

• Denied fever, night sweats, weight loss, or chronic cough.

• Past Medical History: no significant illness, no surgeries or hospitalizations.
Case 1 – History and Physical Exam

- **Family/Social History**
  - Patient lives with mother and 9 y/o brother. A maternal aunt, who spent many days with them, was diagnosed with pulmonary TB last month. All household contacts were tested, but only our patient had a positive TST.

- **Physical exam was completely normal.**
Case 1

5 y/o female with no symptoms and normal exam, but with significant exposure, positive TST and abnormal CXR.

- Would you do any further evaluation?
- Do we need to obtain samples for cultures? What would be the best samples for this patient?
- Would you treat? LTBI vs TB disease?
Case 1 - Results

- Aunt’s sputum was reported as growing M. tuberculosis.
- Gastric aspirates were not obtained.
- HIV antibodies were negative.
- Patient was started on INH, Rifampin and PZA.

Final Diagnosis
Primary Pulmonary TB
Pediatric TB
How cases are discovered

- Active
  - Contact investigation: 25-80%
  - Screening of high risk groups: 3-35%
- Passive
  - Symptomatic children: 15-45%
Pediatric Tuberculosis Clinical Presentations

- Pulmonary TB
  - 75-80% of presentations in children
  - Symptoms depend on the age
  - Infants
    - Fever, persistent cough, decreased appetite, wheezing
  - School-aged children can be asymptomatic or have mild symptoms (e.g. dry cough)
  - Adolescents
    - Productive, prolonged cough (> 3 weeks), with systemic symptoms (fever, chills, night sweats, loss appetite, weight loss)
Pediatric Tuberculosis
Clinical Presentations

- Primary pulmonary TB
  - Typical
    - Primary focus with hilar adenopathy with or without focal infiltrates, usually mild to moderate symptoms (could be asymptomatic)
  - Progressive primary
    - Progression of primary focus to produce extensive pulmonary infiltrates and cavitation, severe symptoms resembling pyogenic pneumonia (rare)
Pediatric Tuberculosis Clinical Presentations

- Chronic pulmonary TB (adult-type)
  - Results from reactivation producing cavitation
  - Usually presents with classic symptoms
  - Rare in young children, but can occur in adolescents
Pediatric Tuberculosis Clinical Presentations

Most cases of TB in children are NOT confirmed bacteriologically

“Clinical Cases”

- History of recent contact to an active case
- Positive TST
- Abnormal CXR and/or physical exam
- No bacteriological confirmation
  - Not done or negative cultures
Case 1 – Pearls

- Asymptomatic presentation is not unusual in school-aged children, even with obvious disease on CXR.
- A negative culture does not rule out TB. Many pediatric cases meet the “clinical case” definition.
- Primary pulmonary TB (hilar adenopathy with/without infiltrate) is the most common presentation in children with TB.
Case 2 – History

- This is a 6-year-old Bosnian male, who presented to ER with one-week history of fever and occasional vomiting. No cough, difficulty breathing or weight loss.

- Social History
  - Patient lives with both parents and a younger sibling. They all immigrated to U.S. from Bosnia about six months PTA. At that time, they all had PPD placed. Both parents tested positive with negative CXR, but elected not to take meds. Both children tested negative (less than 10 mm).
Case 2 – Physical Examination

- T: 103.2°
- P: 154
- R: 24
- BP: 111/70.
- O2 Sat. on RA: 96–97%.

- Patient was awake, alert, in no apparent distress.
- Chest: markedly decreased BS in the right lung field.
- Rest of exam was within normal limits.
Case 2

- He was admitted to the hospital and started on IV antibiotics (Ceftriaxone).

- After 3 days, he continued having daily fever spikes, but without changes in his respiratory status.
  
  - Would you do any further evaluation?
  
  - Repeat TST?
  
  - Do we need gastric aspirates versus sputum?
  
  - Other cultures?
  
  - Other tests?
Case 2 – Hospital Course

- TST was placed and read in 48 hours as 22 mm of induration.
- Induced sputum/early morning gastric aspirates were obtained.
- Chest US showed a loculated, organized pleural effusion.
- Surgery was consulted and they performed a video-assisted thoracotomy and decortication. Pleural biopsy and AFB cultures were sent.
- HIV antibody: negative
Case 2 – Hospital Course

- Patient was started on INH, Rif, PZA and Ethambutol.
- He improved with resolution of fever in three days.
- He was discharged home to continue meds under DOT.
Case 2 – Final Results

- Gastric aspirates X 3
  - AFB smear and cultures were negative
- Induced sputum AFB smear was negative
- Pleural Biopsy
  - Multiple caseating granulomas
- Pleural fluid/biopsy
  - AFB smear and PCR for *M. Tb* were negative
- Sputum and pleural cultures grew *M. tuberculosis*, resistant to INH
Pediatric TB
Pleural TB/Empyema

- Complicates 2-38% of TB in children
- More common in adolescents, rare in preschool children
- Symptoms may mimic bacterial pneumonia
  - Fever, cough, decreased BS
- Pleural fluid
  - Lymphocytic effusion, low glucose, high protein
  - Adenosine deaminase (ADA) >40 U/L
  - Culture + in 20-40%
  - PCR+ in 75%
- Pleural biopsy
  - Most sensitive way to diagnose pleural TB
  - Tissue culture + in 40-60%
Specimen Collection
Which is the best sample in children?

• Gastric aspirates
  – Obtain with NG tube upon awakening the child and before ambulation or feeding

• Problems
  – Invasive
  – Expensive: need for overnight stay
  – One study suggested it can be done as outpatient, but results not duplicated
  – Low yield (<50%)

• Induced sputum
  – Hypertonic saline neb to irritate airway and produce cough
  – Inpatient or outpatient

• Problems
  – Risk of bronchospasm – need to give bronchodiolorators
  – Limited experience in very young children
  – Most centers are not familiar or comfortable with the procedure in children
  – Infection control precautions!
Specimen Collection
Role of Induced Sputum in Children

- Study in South Africa (Lancet 2005; 365: 130)
- Compared the yield of IS with gastric aspirates in young children.
  - Mean age: 13 months (1 mo – five years)
- Induced sputum: salbutamol, followed by 15 min of 5% hypertonic saline neb. Naso-pharyngeal suction
- Results
  - One IS = three gastric aspirates (64-66%)
  - Three IS much better: 87%
- Minor side effects
  - Increased coughing, epistaxis, vomiting, wheezing.
Specimen collection: Which is the best sample in children?

- For young children (less than 5 y?)
  - Gastric aspirates*

- For older children without a productive cough
  - Induced sputum*

- For older children and adolescents with productive cough
  - Spontaneous sputum*

- Culture pleural fluid, CSF, urine, other body fluids and biopsy specimens

* Send samples collected on 3 separate days
Case 2 – Pearls

- TB should be considered in a child with pneumonia, not responding to appropriate antibiotics.
- TST may take up to 10 weeks from exposure to convert.
- It is important to obtain cultures for TB in children, especially when the source case is unknown.
- Induced sputum samples have better yield than gastric aspirates. Consider in children older than five years.
Case 3 – History

• A 15-month old, previously healthy male presented to ER with two-day history of fever, cough and diarrhea. No difficulty breathing, weight loss, or decreased activity.

• Social history
  – Patient lives with mother and an older sister. Mother’s ex-boyfriend used to live with them until a couple of months PTA. He was diagnosed with Pulmonary TB last month. Patient, mother and sister had positive TST with negative CXR. However, they were given an appointment at the TB clinic for the following month.
Case 3 – Physical Examination

- T: 40.1°C
- P: 117
- R: 44
- BP: 89/56.
- O2 Sat. on RA: 96 – 97%.
- Patient was awake, alert, fussy, but consolable.
- Neck: Supple, shotty posterior LN
- Chest: Diffuse rhonchi bilaterally, no crackles or wheezes.
- Abdomen: Distended, with questionable HSM, but hard to evaluate
- Rest of exam was within normal limits.
Case 3

- Would you do any further evaluation?
- Do we need gastric aspirates?
- Spinal tap?
- Other cultures?
- Other tests?
Case 3 – Further evaluation

- Early morning gastric aspirates x 3
- Urine culture for AFB
- LP
  - CSF WBC: 1   RBC: 0
  - CSF Glc: 62   Pr: 12
  - CSF AFB
- HIV antibody: negative
- Abdominal US
Case 3 – Hospital Course

- Patient continued having daily fever spikes, but without changes in his respiratory status
- Patient was started on INH, RIF, PZA, and EMB
- He improved with resolution of fever in two days
- He was discharged home to continue meds under DOT
Case 3 – Final Results

• Gastric aspirates
  – AFB smears were negative times three
  – Two out of three gastric asp. cultures grew Mycobacterium tuberculosis (pan-susceptible)

• Urine culture was positive for M.tb

• CSF culture was negative
Conditions that Increase the Risk of TB Disease

- HIV infection
- Recent infection with M. tuberculosis
  - Infants and post-pubertal adolescents are at increased risk compared to other children
- Substance abuse (especially drug injection)
- Certain medical conditions: malignancies, immunosuppressive therapy, diabetes mellitus, chronic renal failure/hemodialysis, silicosis, low body weight (10% or more below the ideal)
Pediatric Tuberculosis Clinical Presentations

Miliary TB

- Results from hematogenous spread, affecting two or more organs
- Signs and symptoms
  - Fever, malaise, weight loss, night sweats, lymphadenopathy, hepatosplenomegaly, etc.
- 30% may develop meningitis
- TST may be nonreactive
- CXR has a characteristic pattern
Case 3 – Pearls

- Infants and children less than four years of age are at increased risk of developing TB disease once infected.
- When identified in a contact investigation, they should be evaluated and started on treatment promptly.
- When disease occurs, clinical manifestations most often appear one to six months after infection.
- Non-pulmonary sites, including meningitis and miliary TB, tend to be more common among young children and persons with impaired immunity.
Case 4 – History

• A 10 mo old male presented to the ER with a 3 wk h/o runny nose, cough and fever. He received a course of antibiotics without improvement. On that day, mom noticed right retroauricular swelling.

• Physical exam:
  – T: 38.5
  – Awake, alert, but just lying in bed
  – HEENT: right eye deviated laterally, right TM dull with decreased mobility, mild retroauricular swelling
  – Neuro: left-sided paralysis
  – Rest of exam: normal
Case 4

- Head CT: right sided infarct and mastoiditis
- CXR: normal
- LP – CSF
  - WBC: 71 (6N, 90L, 4M); RBC:0
  - Glucose: 22
  - Protein: 149
  - Gram stain: few WBC, no organisms
Case 4

Patient was started on IV antibiotics, but his symptoms did not improve.

- What would you include in his further evaluation?
- Do we need gastric aspirates?
- TST?
- Other cultures?
- Other tests?
Case 4 – Further Evaluation

- CSF sent for AFB studies
  - AFB smear and cx: negative
  - PCR for MTb: negative
- Gastric aspirates x 3
- Middle ear effusion was sent for bacterial and AFB cultures
- TST: 3 mm
- HIV antibody: negative
Case 4 – Hospital Course and Followup

- Patient was started on INH, RIF, PZA and IV amikacin PLUS steroids
- He improved very slowly, but with permanent sequelae.
- Repeat TST a month later: 25 mm
- Source case investigation revealed that his paternal grandmother had pulmonary TB
- Culture results:
  - 1 of 3 gastric aspirates grew M. Tb
  - Middle ear cx: M. Tb
  - CSF Cx: negative
Pediatric TB - Meningitis

- TB of the CNS complicates 0.5 – 2% of pediatric TB cases
- Usually present 2-6 months after primary infection
- Most patients are under 2 years of age
- CNS TB
  - Meningitis 95%
  - Tuberculoma 5%
  - Tuberculous abscess <1%
- Early recognition and therapy has a great impact on outcome
TB Meningitis
Clinical Stages

• Stage 1
  – Patients have no specific systemic symptoms (fever, irritability, nausea/vomiting), are lucid with no focal neurologic signs or evidence of hydrocephalus

• Stage 2
  – Patients are confused or have focal signs, such as cranial palsies and/or hemiparesis

• Stage 3
  – Represent advanced illness with delirium, stupor, coma, and/or dense hemiplegia
TB Meningitis
Diagnostic Studies

- CSF shows elevated protein, low glucose, and mononuclear pleocytosis
- CT evidence of basilar meningeal enhancement combined with any degree of hydrocephalus
- MRI is superior to CT in defining lesions of the basal ganglia, midbrain, and brain stem, and for evaluating all forms of suspected spinal TB
- Microbiologic studies
  - AFB smear: + in 10-30%
  - AFB cx: + in 30-70%
- PCR on CSF had considerable variability in sensitivity and specificity
- Diagnosis usually requires a HIGH index of suspicion
Case 4 - Pearls

- The diagnosis of TB meningitis requires a high index of suspicion
  - CSF showing lymphocytic/mononuclear pleocytosis, low glucose and/or high protein, with negative bacterial cultures
  - Basilar meningeal enhancement plus hydrocephalus on CT
- A negative TST does NOT rule out TB. Children with severe disease will often have a negative TST
- When TB meningitis is suspected, initiate tx promptly. Early treatment has a positive impact on long term outcomes
Case 5: History

- 2 y/o AA male presented to ER with 8 day history of fever and cough. He was diagnosed with pneumonia and was prescribed amoxicillin. After 5 days, his fever was not better, so he was admitted to the hospital for IV antibiotics. He was started on ceftriaxone, and then vancomycin was added. However, fever persisted.

- PMH: no significant illness, no surgeries or hospitalizations
Case 5

- Family/Social history: lives with mother and 2 older siblings. Has attended a Daycare Center since the age of 7 months. No travel history, no history of contacts with adults with HIV, IVDU, homeless, incarcerated.

- Physical exam was normal, with the exception of Tmax of 41 degrees and mild nasal discharge.
Case 5

- TST was placed and read as 10 mm of induration
- Gastric aspirates x 3 were sent
- Patient was started on INH, Rif, and PZA, and fever resolved after 3 days.
- He was discharged home to continue meds under DOT.

  - Gastric aspirate cultures were negative
Case 5

2y/o male with a clinical case of pulmonary TB, but without significant exposure.

What would you do next?
Case 5

Source case investigation

- All household tested negative (TST)
- Investigation was expanded to the Daycare Center (DCC)
- 3 DCC staff had +TST, but neg. CXR
- One DCC worker, had neg TST, but history of chronic cough, and was diagnosed with Pulmonary TB (cavitary, smear positive)

What next?
Case 5

Full scale Contact Investigation

- 52 exposed children were identified and tested (ROS, Physical exam, TST and CXR)
- 24 children had + TST
  - 5 children were diagnosed with Pulmonary TB (1 with meningitis)
  - 18 children had LTBI
- 28 children had - TST and - CXR
  - <5y/o started on window prophylaxis
  - All (except 3) were retested after 10 weeks
  - 2 had +TST
Source-case Investigations

- TB in children <5 years of age typically indicates recent transmission.
- Young children usually do not transmit TB to others. The source-case is usually an adult care-giver.
- If household contacts are neg, expand investigation.
- A source-case investigation should be considered for children <5 (especially <2) with TB.
Day Care Settings: High Priority for Contact Investigation

- Children < 5 years of age
- Prolonged exposure
- Close contact
- Depending on the size of the daycare center
  - Crowding
  - Poor ventilation
Management of Contacts Younger than 5 years of age

• Evaluation
  – TST
  – CXR
  – Review of symptoms and physical exam (PE)

• Primary prophylaxis (“window”)
  – If TST, CXR, and PE are neg, start INH until repeat TST in 8-10 weeks
  – If repeat TST is neg, stop INH
  – If repeat TST is pos, treat as LTBI
Pediatric Tuberculosis
Best Radiographic Studies

- Hilar adenopathy is more common in young children than in older children/adolescents.
- Frontal AND lateral views
  - Lateral views improve the accuracy of detecting hilar adenopathy in children
  - Study in children one month to 12 years of age
    - 27% of hilar adenopathy only detected on lateral films
- AAP recommends both views especially in children less than six years of age being evaluated for TB disease, preferably in all children.
Pediatric Tuberculosis Radiographic Studies

• Role of Chest CT
  – Reported increased sensitivity for detecting hilar adenopathy in children
  – Maybe too sensitive
    • Unclear or no clinical significance
  – Not recommended routinely for asymptomatic children/adolescents with normal CXR
  – Potentially useful in patients with suspicious CXR, especially if symptomatic
Case 5 – Pearls

- The diagnosis of TB in a child is a sentinel event representing recent transmission of TB in the community. A source case investigation should be considered when a young child is diagnosed with TB.
  - Do not forget non-family care-givers
- Daycare centers represent a high priority for contact investigation because of the exposure of very vulnerable children
- Young children are rarely contagious, but the source-case is.
- Use window prophylaxis for contacts < 5 y/o.
Work up for Children with Suspected TB

- History and physical exam
- Tuberculin skin testing (TST) or IGRAs
- Chest x-rays
- AFB smear and cultures
- Additional work up
- Monitoring during treatment
Administering the Tuberculin Skin Test (TST)

- A reaction that develops after 72 hours should be read and recorded as the result.
- TST can be administered during the same visit that immunizations are given, including live-virus vaccines.
- If TST cannot be administered at the same time, it should be deferred for four to six weeks post vaccination (only for live-virus vaccines).
- BCG vaccination is not a contraindication to TST.
Current Recommendations for the Use of TST and IGRAs in Children*

TST is preferred, IGRA acceptable
- Children < 5y of age

IGRA preferred, TST acceptable
- Children ≥ 5 y of age who have received BCG
- Children ≥ 5 y of age who are unlikely to return for TST reading

TST and IGRA should be considered when
- The initial and repeat IGRA are indeterminate
- The initial test (TST or IGRA) is negative and:
  - Clinical suspicion for TB is moderate to high
  - Risk of progression and poor outcome is high
- The initial TST is positive and:
  - >5y of age and history of BCG
  - Additional evidence needed to increase compliance
  - Nontuberculous mycobacterial disease is suspected

* AAP, Red Book 2012
Reasonable Interpretations of Discordant Results

- BCG vaccinated persons > 5 y/o, who are NOT contacts
  - TST reactive but < 15 mm with negative IGRA = false positive

- Low risk situation (why was it done?)
  - Isolated positive result = false positive

- High risk situation
  - Positive result from either of 2 tests = TB infection
Evaluation of a Positive TST or IGRA
LTBI versus Disease

- Review for *symptoms* of tuberculosis
- Physical exam for *signs* of TB
- **Chest X-Ray** – careful interpretation by expert
- If *all* of the above are normal, the diagnosis is LTBI
- If *any* of the above is abnormal, consider work up for TB disease
Chest Radiograph in Children with TB

- Enlarged mediastinal or hilar lymph nodes with or without parenchymal lesions
- Persistent chest pathology not responding to routine antibiotics
Chest Radiograph in Children with TB

- Enlarged mediastinal or hilar lymph nodes with or without parenchymal lesions
- Persistent chest pathology not responding to routine antibiotics
- Rapid and unexplained appearance of a nodular reticular pattern
Chest Radiograph in Children with TB

- Enlarged mediastinal or hilar lymph nodes with or without parenchymal lesions
- Persistent chest pathology not responding to routine antibiotics
- Rapid and unexplained appearance of a nodular reticular pattern
- Pleural effusion
Chest Radiograph in Children with TB

- Enlarged mediastinal or hilar lymph nodes with or without parenchymal lesions
- Persistent chest pathology not responding to routine antibiotics
- Rapid and unexplained appearance of a nodular reticular pattern
- Pleural effusion
- Cavitary lesions (adolescents)
Identification of the source case supports presumptive diagnosis and predicts susceptibilities, but the presumed case is not always the true source case.

Cultures should be obtained in young children when:

- Source case isolate is not available
- Known or suspected MDR TB
- The child is immunocompromised
- Cases of extrapulmonary TB
**Recommended Treatment Regimens for Drug-Susceptible TB in Infants, Children, and Adolescents**

<table>
<thead>
<tr>
<th>INFECTION OR DISEASE CATEGORY</th>
<th>REGIMEN</th>
</tr>
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<tbody>
<tr>
<td>Latent TB infection</td>
<td></td>
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<tr>
<td>Isoniazid-susceptible</td>
<td>9 months of INH daily</td>
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<tr>
<td>Isoniazid-resistant</td>
<td>6 months of RIF daily</td>
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<tr>
<td>INH-RIF resistant</td>
<td>Consult specialist</td>
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If daily therapy is not possible, DOT twice a week may be used for nine months (INH) or 6 months (RIF)

*Red Book 2012*
## Recommended Treatment Regimens for Drug-Susceptible TB in Infants, Children and Adolescents

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<tr>
<td>Pulmonary and extrapulmonary (except meningitis)</td>
<td>2 months INH, RIF, PZA and EMB daily, followed by 4 months of INH and RIF for <em>M. tuberculosis</em></td>
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<tr>
<td></td>
<td>9-12 mo of INH and RIF for <em>M. bovis</em></td>
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- Some experts recommend 3 drugs if source case is pansusceptible, presumed source case has no risk factors for drug-resistance, or child resides in area with low rates of INH resistance.

- Meds can be administered 2-3/week by DOT after the first two weeks to two months.

*Red Book 2012*
Recommended Treatment Regimens for Drug-Susceptible TB in Infants, Children and Adolescents

- For hilar adenopathy only, six months of INH and RIF are sufficient, if drug-resistance is not a concern.
- The optimal treatment of pulmonary TB in children and adolescents with HIV infection has not been established.
  - AAP recommends at least six months.

Red Book 2012
### Recommended Treatment Regimens for Drug-Susceptible TB in Infants, Children, and Adolescents

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<td>Meningitis</td>
<td>2 months of INH, RIF, PZA, and AG or ethionamide or EMB daily, followed by 7 to 10 months of INH and RIF, daily or two/week (9 to 12 months total) for <em>M. tuberculosis</em> At least 12 mo (w/o PZA) for <em>M. bovis</em></td>
</tr>
</tbody>
</table>

*Red Book 2012*
Meningitis/Remarks

- A fourth drug is always given with initial therapy until drug susceptibility is known.
- For patients who may have acquired tuberculosis in geographic areas where resistance to streptomycin is common, capreomycin, kanamycin, or amikacin may be used instead of streptomycin.
- Use of corticosteroids decrease rates of mortality and long term neurologic impairment.
Initial Evaluation

- HIV testing is recommended for all active cases
  - Consider it for LTBI cases
- For adolescents
  - Assess risk factors for Hepatitis B and C
  - Send serologies accordingly
    - Chem: LFTs, renal function, uric acid (PZA)
    - CBC with platelets
- Testing of visual acuity and color vision (ethambutol)
- Routine determination of LFTs is not recommended for children
Recommended Treatment Regimens for Drug-Susceptible TB in Infants, Children and Adolescent

- Evaluation and monitoring of therapy
  - LFTs monitoring is recommended in children with
    - Cases of severe TB
    - Concurrent liver disease
    - Clinical evidence of hepatotoxicity
    - Concurrent use of possible hepatotoxic drugs
    - Pregnancy/postpartum

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Recommended Treatment Regimens for Drug-Susceptible TB in Infants, Children and Adolescents

- Evaluation and monitoring of therapy
  - Monthly clinical evaluations
    - Assess clinical response
    - Assess drug adherence
    - Monitor for signs/symptoms of hepatitis or other toxic effects
    - Visual acuity and color discrimination when using ethambutol.
Thank you!
Merci beaucoup!

[Image of three people smiling]