Elephant Treatment Protocols

Past, Present & Future?

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The Beginning
1997

- Collaboration between USDA, zoo vets, circus vets, 1 human vet
- Goals
  - Develop diagnostic criteria & methods
  - Develop treatment protocols
- Public health issues
  - Risk to humans & animals
  - Address before regulations imposed

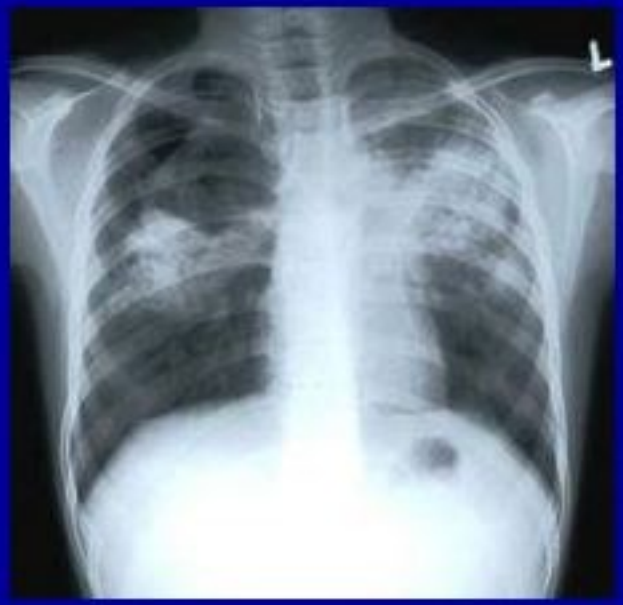
Unanswered questions - 1997

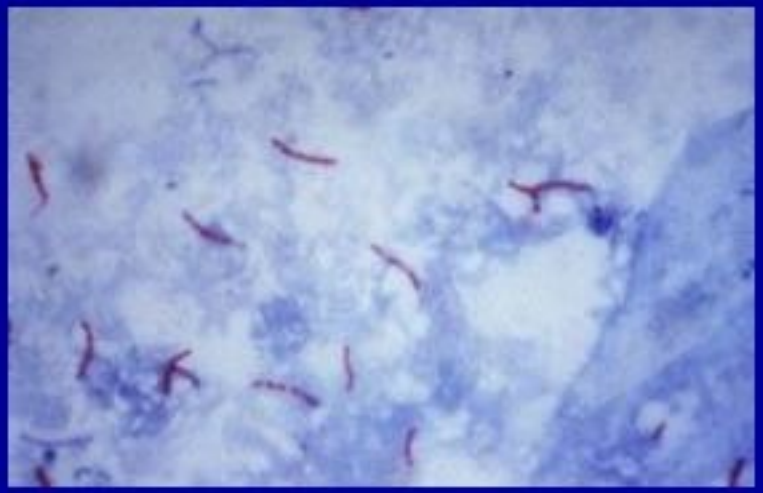
- Natural history of TB in elephants
  - Time between exposure & disease
  - Evidence for latent infection
  - Sites of infection
- Diagnosis
  - How to obtain & reliability of cultures
  - Reliability of skin testing
  - Usefulness of other diagnostic tests
    - Serology
    - Cell-based assays (IFN-γ lymphocyte stimulation)

Unanswered questions - 1997

- Therapeutics
  - Efficacy of TB drugs in elephants
  - Pharmacokinetics
  - Effective dose levels
  - Potential for Cure unknown
  - Adverse effects

Digression to human disease





What can change PK in humans?

- INH - rapid acetylators decreased conc.
- Food minimal effect EXCEPT
  - Colas (sugar & acid) decrease INH
  - Antacids decrease rifampin
- Liver failure & renal failure incr levels

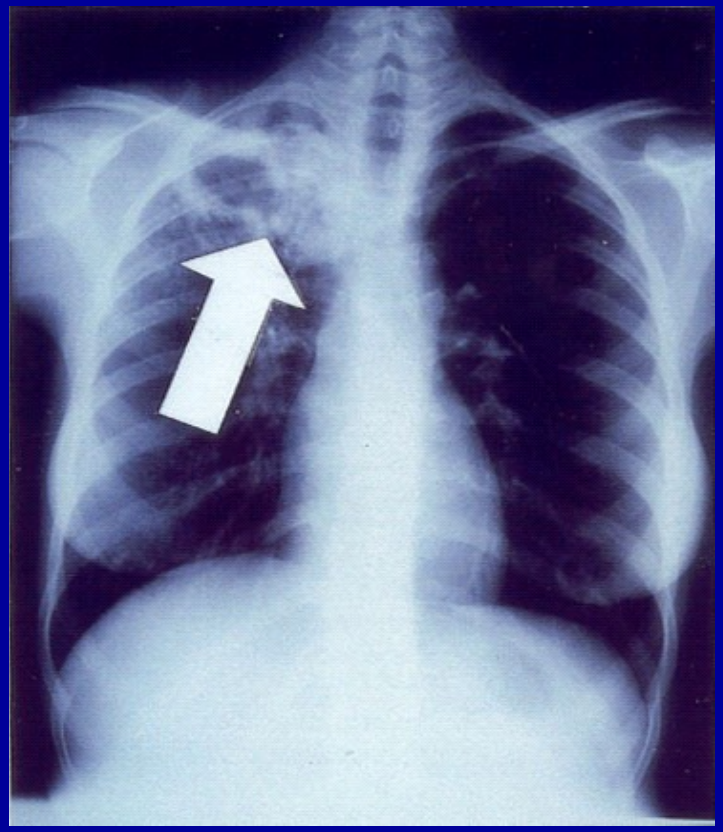
Treatment length in humans

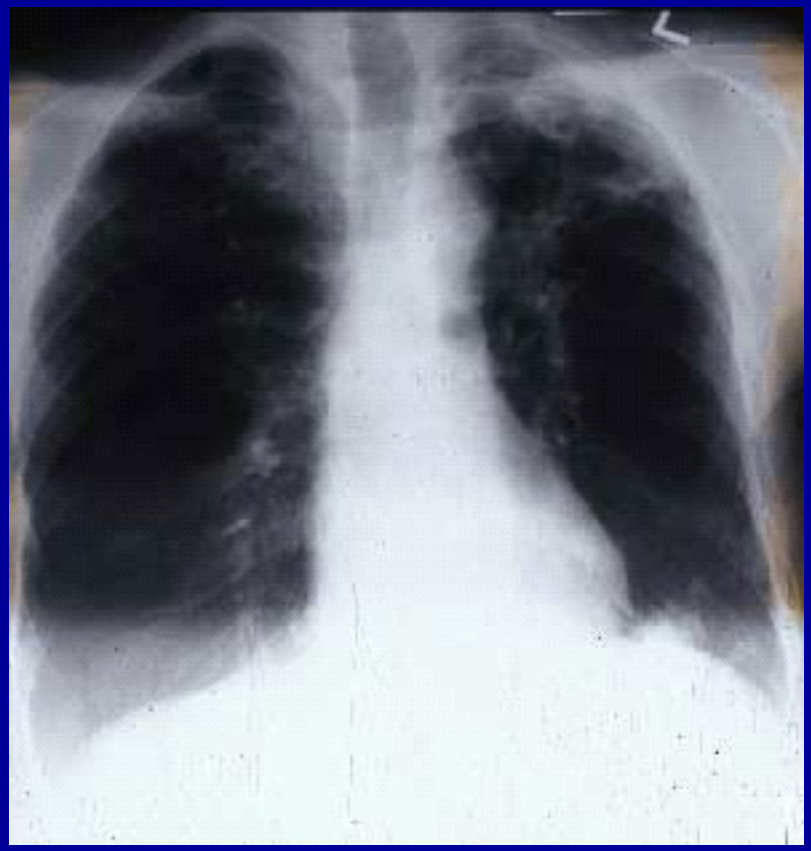
- Pulmonary
  - Uncomplicated: 6 months
    - Need to document sputum clearance
    - Follow clinical response
  - “Complicated”: 6-24 months
  - MDR-TB: 12 months
- Extrapulmonary
  - 12-24 months or until cure
  - 25-40% of cases per post-mortem studies

Complex TB cases

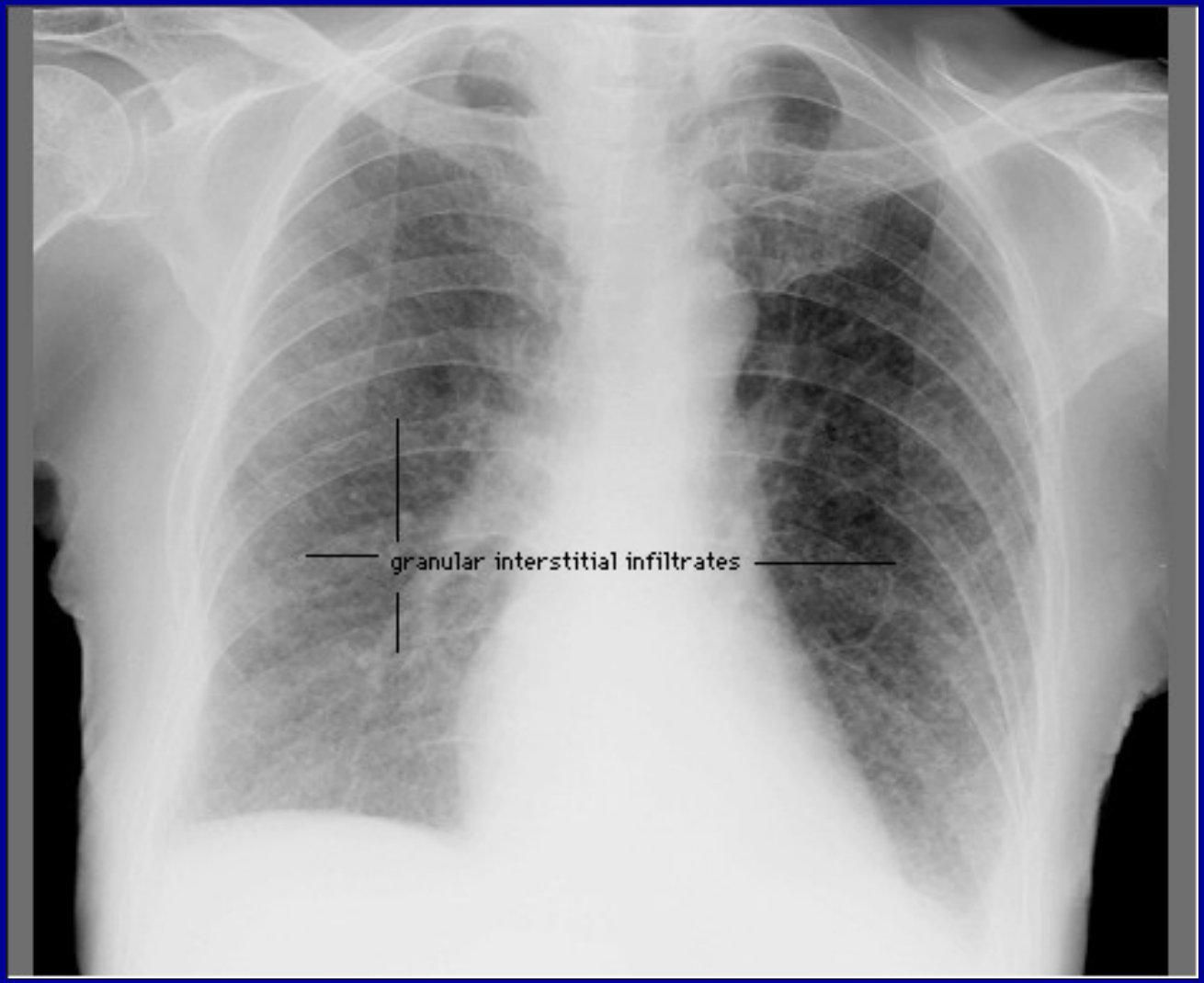
- Pulmonary infection
  - Cavitary (protected focus, high bug burden)
  - Miliary disease (high bug burden)
  - Empyema (requires drainage)
  - Decreased sputum clearance
- Abscess
  - decreased antibiotic penetration
- Bone disease - slower response
- Meningeal & CNS disease
  - poor CNS penetration of drugs

Cavitary TB - high bug burden





Miliary TB - high bug burden



Drug doses in humans

- INH - 300 mg/day (~5mg/kg)
- RIF - 600 mg/day (~8-10 mg/kg)
- EMB - 15 mg/kg/day
- PZA - 15-25 mg/kg/day

Drug targets in humans (mcg/ml)

- Drug levels - based on PK studies
  - INH 3-5
  - RIF 8-24
  - PZA 20-60
  - EMB 2-5
- Used when
  - Clearance is slower than suspected
  - Suspicion of poor absorption (achlorhydria: B12 def, HIV, cachexia)
  - Suspicion of poor adherence
  - Suspicion of fast INH acetylator

Other options

- Fluoroquinolones (PO, $$)
  - Moxifloxacin, Levofloxacin, Ciprofloxacin
- Aminoglycosides (IM)
  - Streptomycin, Amikacin
- Linezolid (PO, $$$)
- New drugs in Phase III trials

Treatment precepts in humans

- PK parameters consistent
- Drug absorption reliable
- DOT (directly observed therapy)
  - Standard of care
  - Assures adherence
- Oral administration always possible

Elephant Guidelines 1998-2003

- Group classification
  - Group D: active infection
  - Group C: exposure to Cx (+) < 1 yr
  - Group B: exposure to Cx (+) 1- 5 yrs
  - Group A: no TB exposure OR exposure >5 yrs
- Group C inapparent vs latent infx
- Group B no vs possible latent infx
- Group A no disease vs unlikely LTBI
  - ***Premise that disease is apparent by 5yrs***

Rx of Active TB Infection (Group D)

- 3 drugs for 2 mos (based on sensis)
- 2 drugs for 10 months
- Tenets / postulates of Rx
  - Poor absorption of 1 or more drugs
  - Inconsistent drug levels
  - Possible extrapulmonary disease
  - Minimum effective Rx unknown
  - Longer Rx provides margin of error

Group C

- Two drugs for 9 months (2003)
  - Increased from 6 months (1998, 2000)
- No travel until 60 doses of adequate Rx
  - Humans: min 2-4 weeks of Rx required to reduce infectivity
  - Elephants: cannot document sputum clearance
  - Reduced ability for “Adequate” Rx = reach target levels
- Not clear whether group C represents
  - Active disease but non-shedding OR
  - Latent TB infection at risk for reactivation OR
  - No infection - since unclear how to diagnosis LTBI

Distant exposures

- Group B - exposure 1-5 yrs
- Group A - no exposure or >5 yrs
  - Assumption that elephant will develop active disease within 5 yrs from exposure
  - Not clear whether such animals have LTBI
  - Serology and current experience calls into question the tenet of “limited” latency - data suggests long latency may exist

PK studies

- Tested INH, RIF, PZA, EMB
- “Real Life” studies
  - Limited, small formal PK studies (*n* = 1-5)
    - EMB best, some PZA & INH
  - Remainder of data sets from treatment attempts
  - Variety of vehicles, additives
  - Stability of drugs varied

INH

- Formulation:
  - Powder >> suspension
  - Suspension affected by age & storage
  - Sugar will inactivate INH
- Route
  - Oral bolus > rectal
  - Over food - useless
- Cmax
  - Oral: 1-2 hrs
  - Rectal: 15 min (range 7.5 - 30 min; NEW info)

RIF

- Formulation
  - Powder > suspension
  - Oral bolus ONLY
- Route
  - ORAL only - no rectal absorption
- Interactions
  - May inactivate steroids
  - No significant food interactions except milk & antacids

PZA

- Formulation
  - Powder > suspension
- Route
  - Oral bolus ~ rectal
- Interactions / food issues
  - None

EMB

- Formulation
  - Suspension (oral)
  - Buffered suspension (rectal)
- Route
  - Oral bolus > rectal buffered susp
- Interactions
  - Non buffered rapidly expelled rectally (buffered suspension is retained)

Other drugs

- Fluoroquinolones
  - Oral suspension (rectal untested)
- Aminoglycosides
  - IM injection
  - Rectal (?) - animal data to support

PK results

	Dose mg/kg	Route	Form.	Cmax (hr)
INH	5	PO	susp	1-2
	4	PO	powder	0.5-1
	4	Rect	susp	0.25-0.5
RIF	10	PO	powder	2-4
PZA	30	PO,R	powder	1-2
EMB	30	PO	powder	1-2

Target serum levels (mcg/ml)

- INH 3-5
- RIF 8-24
- PZA 20-60
- EMB 2-5
  - Based on studies in humans
  - Increased after 1998 to human levels

Dosing (initial)

- INH: 5 mg/kg
- RIF: 10 mg/kg
- EMB: 30 mg/kg
- PZA: 30 mg/kg
  - Each herd tried various treatment methods
  - Different vehicles
  - Oral vs rectal dosing
  - Based on elephant PK data to reach target

Goals of Rx

- Reduce initial sputum bug load
  - Decrease public health hazard
  - Decrease chance of spread to animals
  - Reverse catabolic state
- Reduce risk for resistance
  - 3 cases reported in literature
  - Other anecdotal cases
- Cure if possible

Work left to do

- Full necropsies to define extent of disease
- Better pharmacokinetic studies
- Diagnostic methods to follow Rx
- Need data on efficacy
  - Collate ALL necropsy data
  - Correlate levels with
    - Response to Rx
    - Adverse reactions
    - Cure vs residual disease
    - Define extent of disease

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