Southeastern National Tuberculosis Center
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Learning From the Front Lines: Celebrating 10 Years of the Medical Consultation Database

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The Foundation for The Gator Nation

Objectives

1. Identify opportunities for education of community providers to improve management of persons with TB infection or disease and to stop further transmission of the disease
2. Describe the use of the medical consultation system in the Southeastern United States over the past 10 years to increase provider's knowledge and awareness.
3. Recognize the use of the Medical Consultation Database (MCD) to identify clinical challenges faced in the field to ensure appropriate evaluation and management of patients with TB infection or disease.

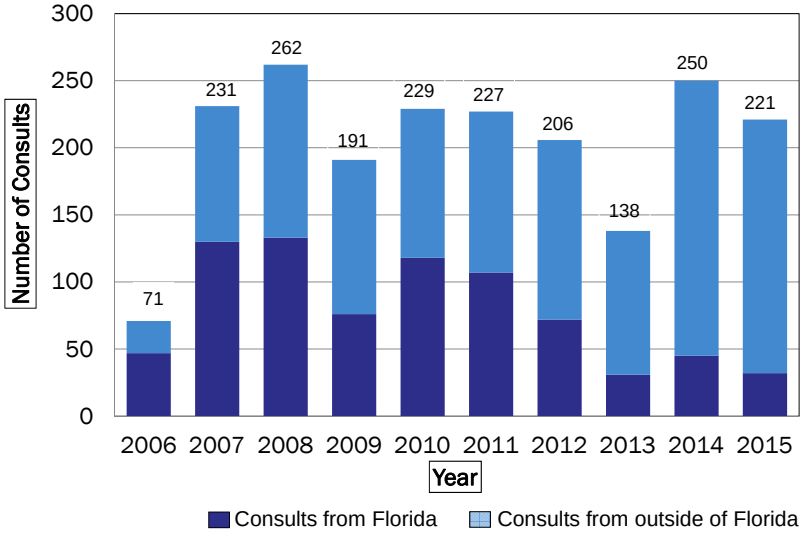
Who are the SNTC Consultants?

- Consultants
  - Dave Ashkin, M.D., F.C.C.P
  - Mike Lauzardo, M.D., MSc
  - Ana Alvarez, M.D.
  - Connie Haley, M.D., MPH
  - Tom Dobbs, M.D., MPH
  - Karen Ferrell, RN, BSN, RM
  - Ellen Murray, BSN,RN
- Other MCD Personnel:
  - Maria Gomez, MCD Administrator
  - Donna Setzer, Product Manager
  - Steve Ryan, Developer

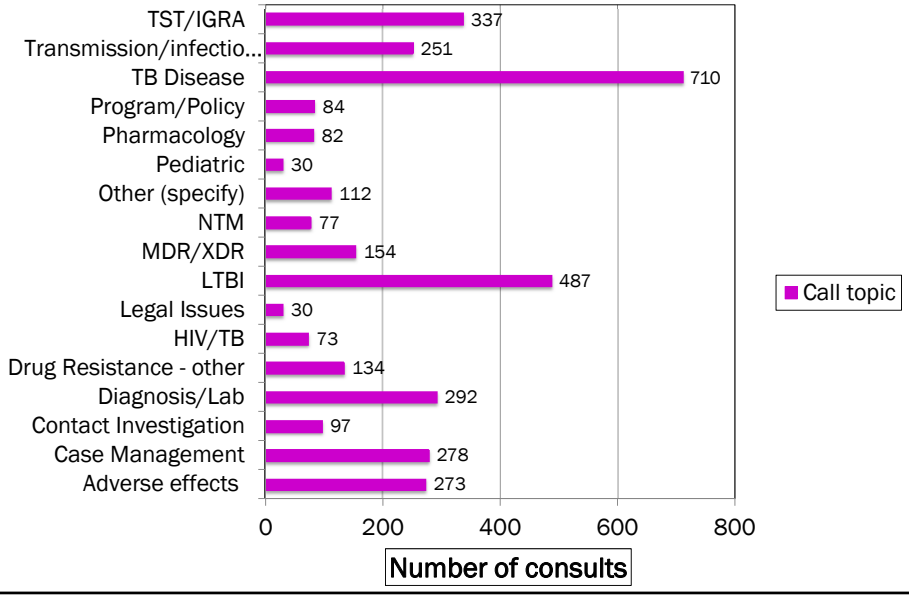
10 years of SNTC Medical Consultations (2006-2015)

- 3,501 documented consults
  - Does not include most consults from Florida, follow up calls for same patient, calls or emails directly to consultants outside of MCD system
  - Also receive email consults from overseas panel physicians regarding pre-immigration diagnosis and treatment
  - We do not take calls from individuals about their own care
  - Documentation has been evolving, now shared with TB control programs
  - CDC encouraging follow up on complex cases

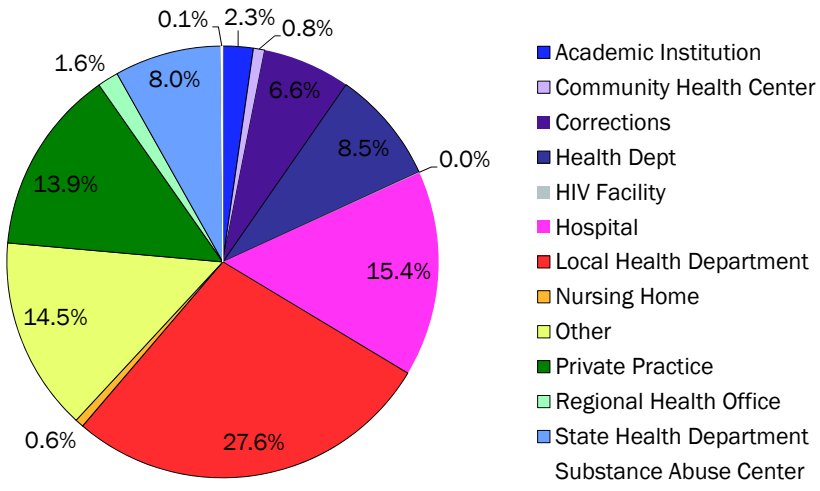
Total MCD Consults through SNTC, 2006 to 2015



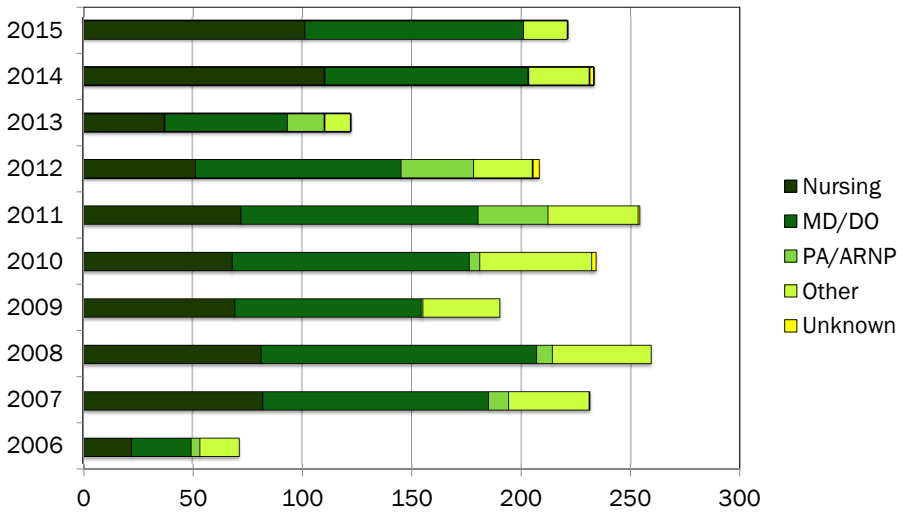
MCD Consults through SNTC by Topic, 2006-2015



MCD Consults through SNTC by Call Setting, 2006-2015



MCD Consults through SNTC by Type of Caller, 2006-2015



MCD CONSULTS

What is the standard for treating a patient for LTBI who is also taking Humira (adalimumab)?

A. Complete a full course of treatment for (latent) TB infection before starting Humira
B. Start LTBI treatment at the same time as Humira
C. Defer Humira until patient is able to complete at least one month of treatment for LTBI
D. Defer Humira indefinitely, the risk of developing TB in TNF-alpha Inhibitor therapy is too high.

Initiation of LTBI therapy and TNF-alpha inhibitors

- CDC LTBI treatment gln last updated in 2000!
- Completing full course of TLTBI before starting TNF-AI would be ideal, many patients not able to wait that long
- Most recommend at least 1 month TLTBI prior to TNF-AA; in some cases can be started concurrently
- Contact rheumatologist to discuss treatment for the other condition
- Published review of LTBI including treatment recommendations for patients taking TNF-alpha blockers:
  - *Vernon A. Treatment of Latent Tuberculosis Infection. Semin Respir Crit Care Med 2013;34:67–86.*

TST performance in patient with Myasthenia Gravis

- Annual physical for an employee who was diagnosed with Myasthenia Gravis two years ago
- Receives prednisone 5 mg every other day and IV gamma globulin 3 times a month, with the last dose 10 days ago.
- Patient states he has had a TST in the past while receiving the IV gamma globulin.
- Both PPD and T-spot were negative in the past.
- Caller wants to know, “is there is information out there regarding the TST or T-spot assay and IV gamma globulin?’

TST performance in patient with Myasthenia Gravis

- Gamma globulin not known to affect the performance of either the TST or IGRAs (interferon-γ release assays)
  - Used as treatment to strengthen the immune response (humoral immunity via a B-cell response), whereas the TST and IGRA are based on T-cell response (cellular immunity) and should not be affected
- T-Spot not extensively researched in this area so little data to definitively answer the question
- Theoretically, IFN-γ response to mitogen used as the positive control in QFT can be considered anergy test, such that if clearly positive the patient is able to mount a T-cell based immune response
- Always consider the presence of comorbidities and treatment provided that could affect a patient’s TST or IGRA results
  - 5mg steroids QOD not a high dose
  - Consider chronic illness, age, nutrition, etc.

Peace Corp Volunteer with a TST conversion

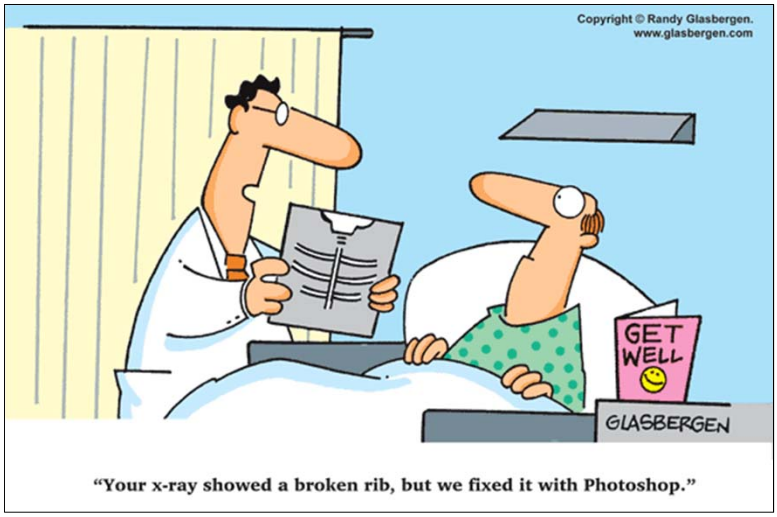
- Peace Corps volunteer has just spent over a year working in Swaziland as a teacher
- Her TST has converted from negative before travel to positive on return
- Swaziland has very high incidence of both HIV and TB
  - Primary MDR 15% and secondary MDR 50%
- Patient reports no knowledge of exposure to anyone with MDR-TB or even anyone who may have been sick

How should you treat this person who converted TST after living in Swaziland?

A. 9 months of INH, self-administered
B. 4 months of rifampin, self-administered
C. 3 months of weekly INH/Rifapentine (3HP) by DOT
D. EMB/FQN for a year for possible MDR prophylaxis
E. Provide education of symptoms of TB disease, but hold treatment since you don't know source TB case and don't want to risk additional drug resistance

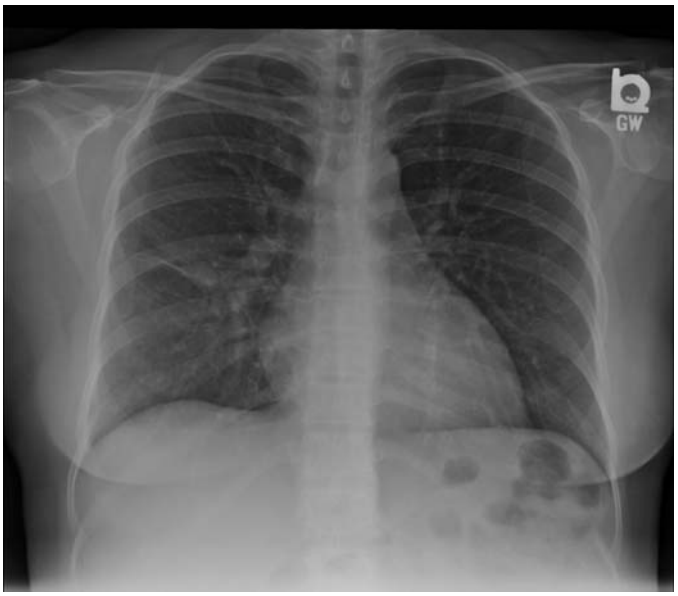
Peace Corp Volunteer with a TST conversion

- Given that the majority of cases in Swaziland are still susceptible to INH and she has no knowledge of exposure to an MDR case, we recommended following CDC recommendations to use INH for 9 months for LTBI treatment.



Pregnant Female with Lung Nodule

- 29 y.o. Female who arrived from El Salvador 07/2014
- Generally healthy, 34 weeks pregnant (EDD 2/4/16)
- No history of TB, no prior treatment, no known exposure to TB
- 9/22/15 she had routine screening during initial OB care and was found to have a positive IGRA
- HIV negative
- Asymptomatic



10/5/15 CXR: 1.7cm nodule right mid lung with adjacent fibrotic linear density.

How should you evaluate pregnant woman with a lung nodule?

A. Wait until she delivers the baby, then evaluate the lung nodule
B. Induced delivery ASAP and evaluate the lung nodule
C. Chest and body CT to evaluate the lung nodule and other possible sites of disease
D. Sputum C&S, empirically treat for TB if smear positive
E. Sputum C&S, wait for rapid molecular testing for resistance before starting TB therapy

Pregnant Female with Lung Nodule (2)

- Sputum samples were collected 10/20, 10/21, 10/22, 11/14/2015 and were smear (-) for AFB
- Unclear if she had rapid molecular testing
  - Nucleic acid amplification test, GeneXPERT, Hain test
- Culture (+) for MTBC samples 10/21, 10/22, 11/14
  - Resistant only to PZA (M. bovis?)
- Baseline LFTs normal
- 11/16/15: TB treatment started with INH/RIF/EMB

- SNTC webinar, "The Raw Milk Movement: How M. bovis is Making a Comeback in the United States" archived 9/18/2015 at https://sntc.medicine.ufl.edu/Webinars.aspx#.VnGcXzZ6rII.
- CDC. Possible Airborne Person-to-Person Transmission of Mycobacterium bovis — Nebraska 2014–2015. MMWR, March 4, 2016 / 65(8);197–201

Pregnant Female with Lung Nodule (3)

- 11/17/15 c/o daily headaches, began taking Tylenol
- 12/9 developed nausea and vomiting, was sent to the ED and was admitted
- LFTs in the hospital:
  - 12/9: AST 344 ALT 582
  - 12/10: AST 403 ALT 604 (TB meds were held)
  - 12/11: AST 260 ALT 642
  - 12/14: AST 161 ALT 413
  - Alk phos was in 162 to 138 range
  - bilirubin remained normal

CDC/ATS/IDSA 2003 guidelines for TB treatment: Liver disease or hepatotoxicity

- Hold INH, RIF, and PZA, all potential causes of hepatic injury
- Serology for hepatitis A, B, and C (if not done at baseline)
- Question patient carefully regarding exposure to other possible hepatotoxins (especially alcohol)
- Can start 2 or more anti-TB meds w/o hepatotoxicity until cause identified
- Once AST level decreases to <2XULN and symptoms have significantly improved, first-line medications restarted sequentially; close monitoring, AST, bilirubin, symptoms

ATS/IDSA/CDC 2003 TB Treatment Guidelines. http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf

CDC/ATS/IDSA 2003 guidelines for TB treatment: Liver disease or hepatotoxicity

- Although INH, RIF, PZA can all can cause hepatitis, because of their effectiveness (esp. INH/RIF), use if at all possible, even if preexisting liver disease
- Treatment options:
  1. **RIF/EMB/PZA for 6 months**, avoiding INH.
  2. **INH/RIF for 9 months**, supplemented by EMB until INH and RIF susceptibility are demonstrated, thereby avoiding PZA.
  3. For patients with severe liver disease a regimen with only one hepatotoxic agent, generally **RIF/EMB, could be given for 12 mo., preferably with another agent, such as a fluoroquinolone, for first 2 mo.**

http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf

Hepatotoxicity of Anti-tuberculosis medications

- Hepatotoxicity risk: INH, Rifampin/rifapentine, PZA, ETA, PAS
- Ethambutol: One report of EMB-related liver cholestatic jaundice, with unclear circumstances; Safe in liver disease
- Fluoroquinolones: Ciprofloxacin and moxifloxacin metabolized in part by the liver, whereas gatifloxacin, levofloxacin, ofloxacin largely excreted unchanged by kidneys.
  - Reversible transaminase elevation among FQ in up to 2- 3% of cases.
  - Severe hepatocellular injury and cholestasis reported to occur <1% of all FQ recipients, excluding trovafloxacin (withdrawn from market)
- Rifabutin: At 150–300 mg/day, hepatotoxicity uncommon per 2006 ATS gls; 2016 Curry guide says risk same as rifampin

Ref: 1. Saukkonen JJ et al. Am J Respir Crit Care Med Vol 174. pp 935–952, 2006.
2. Drug Resistant TB: A Survival Guide for Clinicians, 3rd edition. http://www.currytbcenter.ucsf.edu
3. Devarbhavi and Andrade. Semin Liver Dis 2014; 34(02): 145-161.

Hepatotoxicity of Anti-tuberculosis medications

- Aminoglycosides: Presumed safe in severe liver disease; however, use with caution—some patients with severe liver disease may progress rapidly to hepato-renal syndrome.
- Capreomycin: Presumed safe in severe liver disease; however, use with caution—some patients with severe liver disease may progress rapidly to hepato-renal syndrome.
- Cycloserine: Not associated with hepatotoxicity
- Linezolid: Rarely associated with increased transaminases.
- Imipenem/cilastin: Elevated LFTs noted in up to 6% of patients, but no definite liver damage has been documented.

Ref: 1. Saukkonen JJ et al. Am J Respir Crit Care Med Vol 174. pp 935–952, 2006.
2. Drug Resistant TB: A Survival Guide for Clinicians, 3rd edition. http://www.currytbcenter.ucsf.edu
3. Devarbhavi and Andrade. Semin Liver Dis 2014; 34(02): 145-161.

Treatment of TB in pregnant women

- **Aminoglycosides** are only TB drugs that have well-documented teratogenicity
- **INH**, **RIF**, **EMB** not associated with teratogenic effects
- For pan-susceptible TB during pregnancy, use of **PZA** generally avoided in U.S. due to lack of safety data
  - Recommended during pregnancy by WHO and IUATLD as toxicity to the fetus has not been documented
  - Recommended in drug-resistant TB if isolate susceptible
- **Rifabutin (RFB)**, **CS**, and **PAS** not extensively studied, but animal models and anecdotal human reports have not shown toxicity

Treatment of TB in pregnant women

- Little evidence supporting significant risk to fetus in women who have received FQ for bacterial infections (shorter exposure than with TB).
  - FQ may be safe to use for DR TB in pregnancy if needed, especially after 1st trimester
- Available data for FQ doesn't demonstrate serious arthropathy or other severe toxicity in children
- Poorly treated TB in pregnant women is associated with poor fetal outcomes.
- Benefits of treating TB in pregnancy generally outweighs risk of specific drugs for fetus.

- Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, 3rd edition http://www.currytbcenter.ucsf.edu/products/view/drug-resistant-tuberculosis-survival-guide-clinicians-3rd-edition
- S. Thee et al. Tuberculosis 95 (2015) 229-245.
- Padberg, S et al. Antimicrob. Agents Chemother. August 2014 vol. 58 no. 8 4392-4398.
- Starke JR and Donald PR, eds. Handbook of Child and Adolescent Tuberculosis, 2016. Oxford University Press, New York

Pregnant Female with Lung Nodule (4)

- Hepatitis B & C negative
- Ultrasound: pregnancy progressing normally, fetus is normal but small
- Likely INH Hepatitis (precipitated by acetaminophen?)
- 12/14 patient discharged home
- LFTs repeated 12/17 by LHD: AST 161, ALT 355, alk phos 163, unfortunately she was still taking IRE after discharge
- LHD advised her to hold her TB meds
- Up to this date, she had received 15 doses of IRE

Pregnant Female with Lung Nodule (5)

- Asymptomatic, pregnancy proceeding normally
- LFTs were monitored regularly:
  - 12/22/15: AST 55 ALT266
  - 12/29/15: AST 18 ALT 43 Alk phos 159
- 12/30/15 EMB/RIF restarted
  - 01/07/16: AST 190 ALT 293 Alk phos 185
  - 01/13/16: AST 313 ALT 572 Alk Phos 203 (TB meds held)
- 10 doses RIF 600mg/EMB 1200mg through 01/13/16
- No other reported hepatotoxic exposures (e.g., tylenol, alcohol), possibly due to RIF plus liver effects of pregn?

How should you manage recurrent LFT elevation in Pregnant Female? (due in a month)

A. When LFTs become normal, begin Levaquin/EMB even if before delivery
B. Hold TB therapy until after delivery, then start levaquin/EMB and try to add rifabutin (RBN) as soon as possible
C. Hold therapy until 3 mo. after deliver, restart INH/EMB/RBN

Pregnant Female with Lung Nodule (6)

- Patient induced 1/29—mother and baby did fine
- Placenta was put in formalin without culture for AFB
- Mom seen 2/9/16 in TB Clinic, asymptomatic, AFB cultures (-)
- AST, ALT returned to normal; alk phos remained slightly elevated at 163; bili remained normal.
- Restarted EMB 1200mg then RBN 300mg DOT 5d/wk
  - AST & ALT remained nl, alk phos decreased more slowly
- She plans on breastfeeding for a year or more.
- 2/25/2016 doing well, continue 1yr EMB/RBN 5d/wk

Pregnant Female with Lung Nodule (7)

- Pediatrician evaluated newborn- healthy without TB
- LP done since placental tissue not studied, normal
  - Molecular testing on placenta possible (Fresh or fixed tissue)
  - AFB cultures still negative
- TST was negative, repeat TST planned 8-10 weeks.
- Baby tolerating INH 50mg/d, supplemented with B6 (pyridoxine) 6.25 mg/day, amount should be in a liquid infant multi-vitamin
- Outpatient pediatrician will also monitor the baby's progress

Molecular tests on fixed specimens

- Specialized labs can extract DNA from fixed specimens for molecular identification of MTBC and even molecular DST.
- CDC Infectious Diseases Pathology Branch
  - (http://www.cdc.gov/ncezid/dhcpp/idpb/specimen-submission/index. html) email: Pathology@cdc.gov
- National Jewish Health Mycobacteriology Laboratory
  - http://www.nationaljewish.org/getattachment/professionals/clinical-services/diagnostics/adx/ordering-tests/requisitions/myco_rec_web.pdf.aspx) email: salfingerm@njhealth.org
- U. Washington Medical Center Molecular Diagnosis Section
  - (http://depts.washington.edu/molmicdx/mdx/tests/afbpcr.shtml) email: molmicdx@uw.edu
- Vanderbilt Pathology Laboratory Services
  - Call 1-800-551-5227 or (615) 936-0510

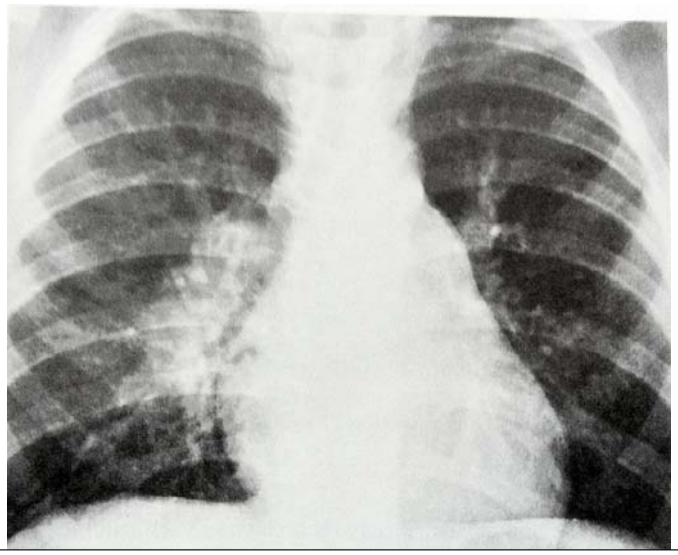
Should you separate mother and infant at birth?

- If mother suspected of having TB disease:
  - Separate until mother and infant receiving appropriate anti-TB therapy, mother wears mask, mother understands and is willing to adhere to infection control measures
  - Once the infant is receiving INH, separation is not necessary unless the mom has suspected MDR TB or has poor adherence to treatment and DOT is not possible
  - Mom can wear surgical mask when holding baby until she is no longer considered infectious
  - Breastfeeding should be encouraged (surgical mask)
    - WHO: breastfeed regardless of mother's status
    - AAP: wait 2 or more weeks until mom not contagious

2015 Red Book® Committee on Infectious Diseases; American Academy of Pediatrics
Handbook of Children and Adolescent Tuberculosis. J. Starke, ed. 2016. Oxford University Press, New York

Child exposed to INH-resistant TB

- 5 1/2 y.o. girl born in U.S. (no BCG)
- TST 16mm
- Potential exposure to adult family friend with INH-resistant TB who visited house while infectious
- She also traveled to Ghana for 3 months
- Mild cough x 1 week, no other symptoms of illness
- 57lbs –95$^{th\%}$ by weight
- Exam: No distress, alert/oriented, age appropriate behavior, lungs clear, one moist cough in 15 min, no bilateral cervical, supraclavicular, or axillary nodes



CXR with R. hilar opacity compared to left. Preliminary radiologist interpretation: “R. hilar adenopathy—should be considered active TB until proven otherwise.”

What is your plan for this 5y.o. child with a positive TST and hilar adenopathy exposed to INH-resistant TB?

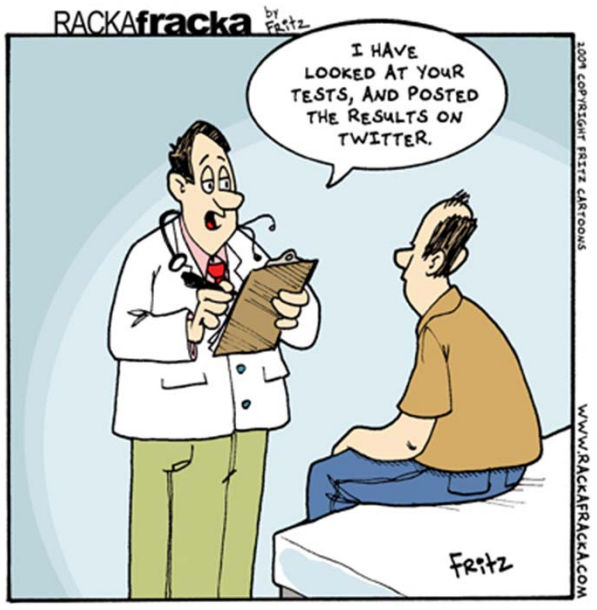
A. Treat with 9 months of INH since this is paucibacillary disease
B. Get a CT scan to confirm the opacity and look for other lesions
C. Sputum induction for AFB culture and susceptibility (C&S)
D. Hospitalize the patient to obtain gastric aspirates for C&S
E. Empirically treat this patient for TB disease given risk factors and clinical findings

Child exposed to INH-resistant TB (2)

- Given history, TST (+), abnormal CXR, consider this TB
- Source case not certain, obtain AFB C&S (x3)
  - At her age, spontaneous sputum collection not recommended, but induced sputum has better yield than gastric aspirates if she can follow instructions
  - If she is not able, hospitalize for early am gastric aspirates
    - Yield of gastric aspirates is <50%
- Baseline eye exam, CMP, CBC, HIV
- With uncertain source, use INH + RIF/PZA/EMB (adjust if culture (+), susceptibilities known)
- If cultures negative, complete 6 mo. RIF/PZA/EMB
  - Rare optic neuritis in young children with nl renal function, monitor visual acuity, red/green discrimination monthly

Persistent hilar adenopathy in children treated for TB

- For most patients with pulmonary TB, CXR should be obtained after 2 mo. therapy to evaluate response if pulmonary infiltrates or cavitation; CXR is also recommended at end of treatment.
- In children with hilar/mediastinal adenopathy without infiltrates, repeat the CXR at the end of therapy only.
- Even with successful 6-mo. regimens, hilar adenopathy can persist for 2 to 3 years so a normal CXR is not necessary to discontinue therapy.
- Follow-up CXR after successful therapy is usually not necessary unless clinically indicated (e.g. clinical deterioration).



60 year old woman on inhaled steroids

- 60 y.o. woman with a remote history of having a positive TST result
- She was subsequently diagnosed with cough variant asthma
- She declines steroid inhaler recommended by physician due to fear it will activate her TB
- Her provider has consulted you to ask, “Can inhaled steroids be administered to an adult with positive TST?”

Can inhaled steroids be administered to an adult with positive TST?

A. Yes
B. No
C. I’ve been wondering about that….

Can inhaled steroids be administered to an adult with positive TST?

- Inhaled corticosteroids (ICS) preferred to oral corticosteroids (OCS) because anti-inflammatory effect directed at airways, reducing risk of unwanted systemic effects
- Whether ICS use increases risk of developing TB controversial
- Observational studies using insurance claims data:
  - Brassard et al. Exposure to ICS not associated with risk of TB in presence of OCS but is associated with increased TB risk in nonusers of OCS, especially at high exposure levels (Quebec)
  - Chung et al. 2-fold incr. TB risk, dose-response effect of ICS in Taiwan
  - Didn't control for TB risk factors such as country of birth, ethnicity, socioeconomic status, recent contact with TB disease, TB associated abnormal findings on CXR, HIV status
  - Several other observational studies linking ICS to increased risk of TB in patients infected with M. TB, No definitive randomized trials

Brassard et al. Am J Respir Crit Care Med 2011; 183: 675–8.
Chung et al. Int J Clin Pract, October 2014, 68, 10, 1193–1199

Can inhaled steroids be administered to an adult with positive TST?

- ATS/CDC gls: 15 mg/d or more of oral prednisone (or its equivalent) administered 1 month or longer a risk factor for TB.
- Jick et al: risk of TB was significantly increased at doses as low as prednisone 7.5 mg daily
- Fluticasone 1,000 mg/d or more estimated to be equivalent to approximately 10 mg of prednisone per day when the systemic effect is evaluated by suppression of serum cortisol.
- Regardless of actual risk, if patient or provider have concerns about inhaled steroids, patient should be offered LTBI therapy to decrease her chances of developing active TB disease.
- No recommendations to screen ICS users for TB infection

ATS/IDSA/CDC 2003 TB Treatment Guidelines. http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf
Jick et al. Arthritis Rheum 2006;55:19–26

"The defibrillator's not working! Quick, everyone scuff your feet on the carpet!"

Sudanese male with lymphadenopathy

- 42 year old male from Sudan, immigrated to U.S. in 2005
- 08/15, presented to hospital c/o 1-2 mo. fatigue, weight loss, superficial upper R. chest wall sternoclavicular mass
- Received antibiotics and was discharged home
- 11/15, returned to hospital c/o that "more lumps" had developed in his neck, and new oropharyngeal abscess.
- IGRA (+)
- CXR and CT: multiple enlarged cervical, hilar and mediastinal lymph nodes
- Empirically started on TB meds, PZA incorrectly dosed
- Chest wall mass aspirated; grew M. TBC; DNA probe results never received

Sudanese male with lymphadenopathy (2)

- Referred to TB Clinic, RIPE started appropriate doses, 5d/wk
- Rapid clinical improvement in his fatigue and weight loss
- In 3-4 wks, oropharyngeal, neck/chest wall masses resolved
- All sputum cultures negative (11/15/16). HIV(-). Labs OK.
- He received 40 doses of 'daily' RIPE (8wk)
- 01/19/16, began continuation phase INH 900mg/RIF 600mg assuming full susceptibility though results not yet received
- 02/02/16 preliminary results susceptible to RIF, EMB, PZA
- 3/30/16 finally received preliminary INH susceptibilities which reported resistance at 0.1mcg/ml
- He received 18 doses intermittent INH/RIF, improving

How should treat this patient with low-level INH resistant TB?

A. Stop INH, restart RIF, EMB and PZA five days per week to complete the remainder of 6 months (count INH/RIF)
B. Stop INH, restart daily RIF, EMB and PZA to complete 6 mo. regimen, but don't count INH/RIF doses
C. Stop INH, restart BIW RIF, EMB, PZA to complete 6 mo. but don't count INH/RIF doses
D. Stop INH, restart RIF/EMB/PZA and add a fluoroquinolone to complete 6 months
E. Continue INH 900mg/RIF 600mg (high-dose INH) to complete the 6 month course since isolate is susceptible at 0.4mcg/ml

ATS 2003 guidelines for TB treatment (INH resistant or not tolerated)

- INH important first-line TB drug because of potent early bactericidal activity vs. rapidly dividing cells; Combination therapy with INH prevents selection and emergence of drug-resistant TB population
- Resistance to isoniazid is the most common drug resistance among all of the first-line drugs, with an estimated prevalence of 13% worldwide, including new (~10%) and re- treatment cases (~28%)
- Data from Hong Kong BMRC study suggest that in the presence of INH resistance results are better when PZA is used throughout

❖ When INH can't be used or organisms INH-resistant, 6-mo. RIF, PZA, & EMB nearly as efficacious as INH-containing regimen (**Rating BI**)

❖ **Alt: RIF/EMB 12 mos, preferably with PZA** ≥ init. 2 mo. (**Rating BII**)

-ATS/CDC/IDSA TB Treatment Gls http://www.cdc.gov/mmwr/PDF/rr/rr5211.pdf
-Hong Kong Chest Service/British Medical Research Council. Am Rev Respir Dis 1987;136:1339–1342.
-Mitchison DA, Nunn AJ. Am Rev Respir Dis 1986;133:423–430.
-Zierski M. Lung 1977;154:91.

High-dose Isoniazid

- Most INH resistance conferred via *katG* or *inhA* mutations
  - *katG* → high-level INH resistance (1.0 mg/mL solid media)
  - *inhA* → lower levels INH resistance (0.2 mg/mL), Ethionamide cross-resistance
- Theoretically possible to overcome low-level resistance by increasing the dose of INH
  - INH (standard dose) associated with better survival rates in patients with W-strain of MDR-TB susceptible to higher INH conc.
  - Double-blind RCT high-dose INH (16-18 mg/kg) vs. placebo plus SLD , those who received high-dose INH were 2.38 times more likely to convert cultures to (-) than those on placebo, and they had a 2.37 times higher rate of being culture negative at 6 months.

Drug-Resistant TB: A Survival Guide for Clinicians, 3rd ed,
-Isolated Resistance to INH (Ch. 4)

- Optimum regimen of INH mono-resistant TB is unknown, but effective treatment regimens are available.
  - 2009 systematic review/meta-analysis by Menzies, et al., found that among pts with INH mono-resistant TB, outcomes improved with longer duration RIF & PZA, daily treatment (not intermittent), greater #s of effective drugs
  - U.S. studies reported relapse rates 2-5% using 3- to 4-drug regimens administered ≥6 mos. However, 26-59% had treatment discontinued or duration extended because of drug-related adverse reactions, usually assoc. with PZA

http://www.currytbcenter.ucsf.edu/products/drug-resistant-tuberculosis-survival-guide-clinicians-3rd-edition/chapter-4-treatment
- Menzies D, Benedetti A, Paydar A, et al. *PLoS Med.* 2009; 6(9): e1000150.
- Reves R, Heilig CM, Tapy JM, et al. *Int J Tuberc Lung Dis.* 2014;18(5):571-580.
- Cattamanchi A,Dantes RB, Metcalfe JZ,et al. *Clin Infect Dis.* 2009:48(2):179-185.

Drug-Resistant TB: A Survival Guide for Clinicians, 3rd ed.
-Isolated Resistance to INH (Ch. 4)

- Evidence for treatment of INH-resistant TB (con't)
  - Treatment outcomes do not differ based on whether the isolate has low- or high- level INH resistance *in vitro*.
  - Addition of FQ was associated with improved outcomes in studies from Taiwan and Republic of Korea.
  - RIFAQUIN trial: Daily RIF/EMB/PZA/MFZ (moxifloxacin 400 mg) for 2 mo. followed by once-weekly MFX and high-dose rifapentine (RPT) (1200 mg) for 4 mo., (6 months total) as effective as std 6-mo. regimen in drug-susceptible TB.
    - 6-mo. regimen should also be effective for INH mono-R TB *as long as isolate is susceptible to fluoroquinolones.*

http://www.currytbcenter.ucsf.edu/products/drug-resistant-tuberculosis-survival-guide-clinicians-3rd-edition/chapter-4-treatment
- Wang TY, Lin SM, Shie SS, et al. PLoS ONE. 2014:9(1):e86316.
- Huyen MNT, Cobelens FGJ, Buu TN, et al. Antimicrob Agents Chemother. 2013;57:3620-3627.
- Jindani A et al N Engl J Med. 2014 Oct 23;371(17):1599-608.

Drug-Resistant TB: A Survival Guide for Clinicians, 3rd ed.
-Isolated Resistance to INH (Ch. 4)

Based on current evidence, 3 txt options for INH-R TB:

1. **Daily RIF/EMB/PZA (± FQ)**, all given for 6-9 mos depending on microbiologic, clinical, radiographic response to tx
   - If initiated std 4-drug regimen, stop INH continue RIF/EMB/PZA
   - Continuation of INH with documented INH mono-resistance not necessary, given the high cure rate with this regimen
   - FQ may be added, esp if extensive and/or cavitary ds (if suscept)
2. If can't tolerate PZA, **use RIF/EMB+Levo or Moxi 9-12mos.**
   - Confirm FQ susceptibility
3. **Daily RIF/EMB/PZA/MFX (400 mg) for 2 mos followed by once-weekly MFX and high-dose RPT (1200 mg) for 4 mos**
   - Confirm FQ susceptibility.

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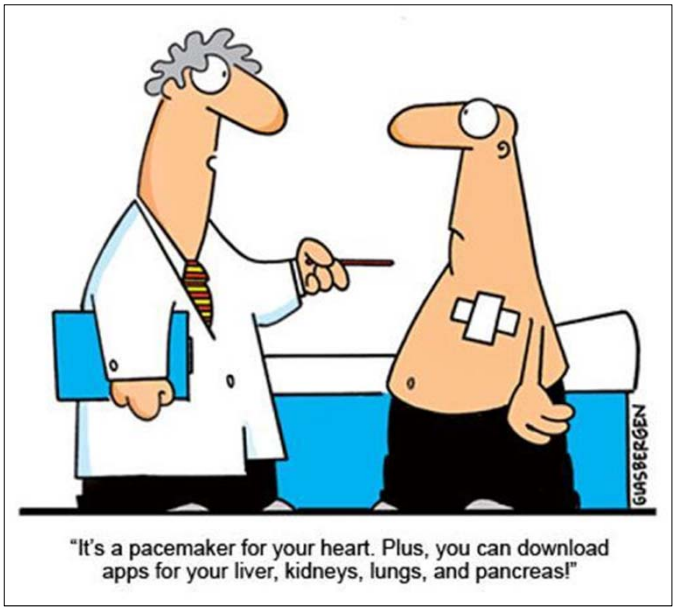
How should treat this patient with low-level INH resistant TB?

- Intermittent regimens facilitate DOT, which markedly improves TB treatment adherence and outcomes
- Study of patients in US and Canada with pulmonary and EP TB and INH intolerance or resistance;
  - Intermittent RMP/PZA/EMB (BIW or TIW following 14d daily tx) appears effective in HIV (-) patients, poorly tolerated, possibly due to prolonged PZA.
    - Reves R, Heilig CM, Tapy JM, et al. *Int J Tuberc Lung Dis.* 2014;18(5):571-580.
- In this patient with INH mono-resistant TB, added potential toxicity of continuing high-dose INH with RIF/PZA/EMB is not likely beneficial.
- No data for intermittent high dose INH plus Rifampin BIW or TIW to support that regimen for INH mono-resistant TB



"It's a pacemaker for your heart. Plus, you can download apps for your liver, kidneys, lungs, and pancreas!"

Adolescent with TB and uncertain infectiousness

- Healthy 13 y.o. with body habitus like an adult, developed primary TB after exposure to an adult with active TB.
- Cough and other "cold" symptoms for a week, positive IGRA
- CXR had some "Pediatric components" such as large pilar lymphadenopathy and no cavitation, but also had "adult-like features" of pleural effusion and disease in superior division of contralateral lower lobe.
- No sputum samples obtained since cough resolved even before TB treatment began.

Should a contact investigation should be done for this 13 y.o. with TB and both adult and pediatric features?

A. No, without a cavity and forceful cough there is little risk.
B. Yes, because the adolescent is adult size and has pulmonary infiltrate.
C. Collect sputum samples for smear, culture, NAAT and use that information to make a decision regarding contact investigation at the school.
D. I'm not sure???

Adolescent with TB and uncertain infectiousness

- Obtain sputum samples x3 for AFB C&S (induced).
- Obtain NAAT on at least one of them.
- If smear and/or NAAT positive, would initiate CI and use initial results to inform need for expansion
- If smear and NAAT negative, adolescent is not likely infectious
- CI also recommended if CXR demonstrates cavities in the lung even if AFB smear negative (not the case here)

CDC. Guidelines for the Investigation of Contacts of Persons with Infectious TB: Recommendations from the NTCA and CDC. MMWR, 2005; 54 (No. RR-15)

"I'd like you to eat more fruit and vegetables, but they're not covered by your health insurance plan."

Inmate with prolonged positive sputum culture (1)

- 22 y.o AA M prison inmate
- History of "underdeveloped lungs" from birth,otherwise healthy; no other TB risk reported
- 1/22/15 admitted to prison infirmary >40lb wt loss in 6 mo., FV, tachycardia, productive cough, SOB, N/V
- HIV nonreactive, RPR nonreactive, Pre-albumin 6.9
- PPD was negative; QFN Gold was positive
- CXR: bilateral diffuse advanced lung disease, bullae and blebs throughout LUL and mid lung, alveolar nodular pattern in remainder of lung. No masses
- 1/29/15: AFB Smear 4+, culture positive M. tb

Inmate with prolonged positive sputum culture (2)

- 1/30/15: CT Scan Chest – Constellation of findings suggest sarcoidosis with extensive pulmonary involvement without significant lymphadenopathy. Other possibilities include military TB.
- 1/30/15: Began RIF 600 mg, INH 300 mg, EMB 800 mg, PZA 1000 mg po daily x 8 weeks
- Levaquin and Prednisone were added for 'SIRS'

Inmate with prolonged positive sputum culture (3)

- 2/9/15: CXR – Diffuse bilateral lung disease including bullous changes in the LUL with worsening areas of opacity when compared with 1/22/15 with increasing left pleural effusion
- Positive cultures 2/6, 2/12, 2/17, 2/19
- 2/17/15: CXR – slight further opacifaction and now with mild relative volume loss in RUL compared to 2/9/15 with no change in the remainder of the chest and slight improvement in the left pleural effusion.

Inmate with prolonged positive sputum culture (4)

- 2/22 - 3/31/15 hospitalized for persistent fevers
- TB susceptibility to all 4 drugs
- Switched to INH/RIF (hadn't completed 2 mo. PZA)
- Drug levels sent to outside lab- all drug levels "low"
- Started on daily IV meds: RIF 600 mg, INH 300 mg, switched to po and sent back to prison
- Smear and culture positive throughout April at CF
- Continuing to have intermittent fever

Why is patient with pan-susceptible TB not responding to treatment?

A. He has a secondary infection or underlying malignancy that is confusing the clinical picture
B. He has acquired new drug resistance
C. He is not absorbing his TB medications
D. Possible IRIS after stopping predisone given at initial diagnosis
E. Something else

Inmate with prolonged positive sputum culture (5)

- 4/22 – 5/6/15 Hospitalized again to eval renal abscess on US, prolonged smear positivity and fevers (almost 3 months)
- Extensive work up for other causes of infection
- 5/5/15 Restarted 5 drug regimen for TB
  - PZA 1000 mg po
  - EMB 1200 mg po
  - Moxifloxacin 400 mg po
  - RIF 600 mg IV
  - INH 300 mg IV + B6 50 mg po

Inmate with prolonged positive sputum culture (6)

- ~15% of patients can have persistent fevers >2 months, even when patient otherwise responding
- Extensive work up in the hospital found no other cause for the fevers
- Consider malabsorption, acquired drug resistance, non-adherence
- Repeat cultures AND susceptibilities, GeneXpert or Hain test for rapid result
- If your state lab does not perform rapid molecular tests, we can have sample sent to UF lab

Inmate with prolonged positive sputum culture (7)

- Now that he has restarted therapy, make sure he has 8 weeks of PZA
- If no RIF resistance, probably don't need FQ
- Check doses for weight; avoid antacids with meds
- Oral meds are fine (no IV)
- Continue daily DOT 7 days, get drug levels at 5th dose
- Keep chart of AFB smears/cultures
- Carefully review DOT with anyone providing it

When to order Therapeutic drug monitoring (TDM)

- AG/CM serum concentrations esp. with renal impairment
- CS concentrations to min risk of CNS tox and optimize dose
- Known or suspected malabsorption (e.g., DM, GI disorders)
- Lack of expected clinical response (at 2-3 mo.) or relapse while on appropriate drugs and doses administered by DOT
- Patients with few effective drugs in their regimen, in order to optimize the effect of available drugs
- Patients with potentially significant drug-drug interactions such as rifamycins and antiretrovirals
- EMB concentrations in patients with sign renal impairment
- In drug resistance, to routinely monitor certain TB drug concentrations in anticipation of toxicity and to escalate a drug dose when possible.

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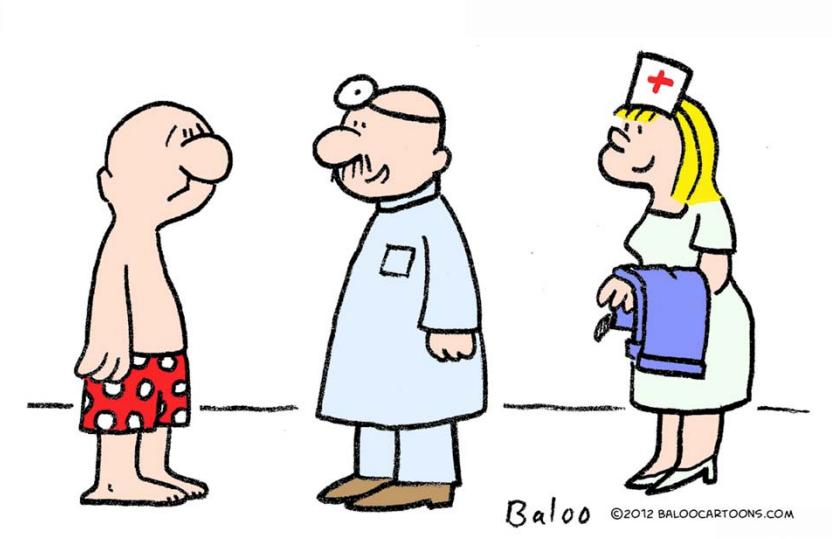
Inmate with prolonged positive sputum culture (8)

- Therapeutic drug monitoring: negative to trace levels on meds
- What is most common cause of treatment failure (and resistance)???

- NON-ADHERENCE!!!!

- Had a very LONG discussion about DOT, referred her to Ellen Murray☺



"The nurse will return your pants as soon as you pay your bill."

QUESTIONS???

Thank You!

1-800-4TB-INFO