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New TB test to detect more people who need DR-TB treatment

MSF report says fixing drug supply and price problems is urgent.

Geneva/Johannesburg – A promising new diagnostic test will finally help detect more people with drug-resistant tuberculosis (DR-TB), increasing the urgency to solve major problems around the pricing and supply of DR-TB medicines, according to a new report by the international medical humanitarian organisation Médecins Sans Frontières (MSF).

DR-TB is on the rise, but less than seven percent of 440,000 new cases each year receive treatment, and DR-TB kills 150,000 people annually.

The treatment of DR-TB relies on old antibiotics, many of which have severe side effects, ranging from constant nausea to deafness, and must be taken as complex regimens – patients must take up to 17 pills every day for up to two years. However, these are the only drugs that exist today that can tackle DR-TB. MSF's report shows that these drugs are riddled with persistent supply and price problems that must be urgently addressed.

"Patients have been stuck in a vicious circle – not enough people are diagnosed, and drug supply problems along with high prices stand in the way of putting more people on treatment," said Dr. Tido von Schoen-Angerer, Executive Director of MSF's Campaign for Access to Essential Medicines. "The low demand for DR-TB drugs has made the market unattractive for producers, which is reinforcing supply and price problems."

DR-TB drugs under the microscope



MSF's report examined medicines used to treat DR-TB according to the number of suppliers, quality assurance and price, based on information obtained from the Global Drug Facility and drug manufacturers. It found that four of the recommended medicines are available from only one quality-assured source. Relying on a sole supplier whose production could be disrupted or stopped at any time always carries a risk of dangerous treatment interruption for patients.

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For example, supplies of the injectable drug kanamycin were disrupted during 2010, leading to a temporary global stockout.

Additionally, MSF's report found that several DR-TB medicines are very expensive, with prices for two drugs having increased by more than 600 percent and one drug by more than 800 percent over the last decade. A 24-month DR-TB treatment regimen can cost as much as US\$9,000 for one patient – 470 times more than the \$19 per patient it costs to cure standard, drug-sensitive TB.

"Now that we have a new test that can detect DR-TB in less than two hours instead of three months, we're going to see many more people who will need reliable drug supplies to get cured," said Dr. Jennifer Hughes of MSF in Khayelitsha, South Africa. MSF is rolling out the new Xpert MTB/RIF test in 15 countries this year. "We need to see some immediate action to resolve these problems and improve access to DR-TB drugs so that more people are started on treatment and transmission of this disease is reduced," said Dr. Hughes.

One way to kickstart increased production of some of these drugs is for donors to guarantee purchase volumes for several years to producers upfront. Other mechanisms such as better forecasting of the mid- to long-term needs for DR-TB drugs are also needed to help attract more producers to the market, to improve supply security and increase competition that helps bring prices down.

"We have developed a model of managing DR-TB within the community that can be scaled up to allow increased access to treatment in high-HIV prevalence settings. With faster diagnosis and better treatment models of DR-TB we need to fix the supply and price issues with DR-TB drugs. We also need to see new drugs developed", Dr Hughes said.

WORLD TB DAY Press Release



National TB Controllers Association Honors Regional Partner

This is the second year the National TB Controllers Association (NTCA) will be honoring individuals or organizations for their dedication and distinguished service in the field of tuberculosis. We respectfully nominate Ken Jost, for the **Ed Desmond Award**. Ken personifies

each characteristic identified in the descriptive associated with the award. Although we note his scientific achievements, his impressive knowledge of tuberculosis and the laboratory, his brilliance as an educator of the public health workforce and the wisdom he shares as a member of numerous workgroups, we especially want to recognize the dedication, care and concern he has for individuals whose lives are impacted by tuberculosis.

Continued on next page

The **MISSION** of the Heartland National TB Center is to build capacity with our partners. We will share expertise in the treatment and prevention of tuberculosis by: developing and implementing cutting-edge trainings, delivering expert medical consultation, providing technical assistance, and designing innovative educational and consultative products.

NTCA: Ed Desmond Award (Ken Jost) continued

"He is willing to help, even when it is something extra if that ends confusion surrounding a particular case, if it gets the susceptibility results earlier, if it means excluding disease in a patient at risk, or identifying a cluster of cases the needs to be evaluated as a possible outbreak. He gets it, he cares about the service the laboratory provides and how essential it is to obtaining good TB outcomes."

"He is more than an excellent microbiologist, he is a dedicated fighter of tuberculosis, the disease, and a champion of excellent TB outcomes for patients and TB programs."

**Introducing the addition of
Enrique (Hank) Benavides
to the Heartland National TB Center Staff**



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The Heartland National TB Center (HNTC) in San Antonio is pleased to announce the addition of Enrique (Hank) Benavides Sr., to the staff. Enrique joined the staff as an Administrative Assistant on June 6, 2011. He is a retiree from the Department of State Health Services. Enrique worked twelve years at the Texas Center for Infectious Disease as a Property Coordinator and continued in this capacity for the San Antonio State Hospital for an additional five years. After seventeen years of service to the State, Enrique retired on June 30, 2010. Enrique also has additional experience servicing the private sector, county, and school districts. He has worked for IBM, Harlandale ISD, San Antonio ISD, and the Tax Assessor's Office. Enrique brings to Heartland substantial experience in administrative work, communication skills, and office ethics. Enrique is also fluent in Spanish and English.

**The VISION of Heartland National TB Center is
to provide *excellence, expertise, innovation* in training, medical
consultation, and product development to reduce the impact of
tuberculosis in our region.**

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CASE PRESENTATION:

Robert Petrossian; Deepa R. Ovian, MD; William A. Agger, MD

CASE HISTORY

A 40 year old Native American male with a 1 year history of untreated HIV infection presented with shortness of breath, productive cough and fever of 6 weeks duration. He was noted to have cervical and axillary lymphadenopathy on exam. The chest radiograph showed densities compatible with interstitial pneumonitis and his sputum was acid fast bacilli (AFB) smear and culture positive for *M. tuberculosis* which was susceptible in vitro to all first line antituberculosis medications. An axillary lymph node biopsy showed caseating granulomas with numerous acid fast bacilli consistent with TB lymphadenitis. The CD4 count was 131 cells/ul. Following initiation of treatment with standard antituberculosis therapy, INH, rifampin, ethambutol, and PZA daily, his symptoms progressively improved. Two weeks after starting TB medications, Atripla (combination tablet consisting of efavirenz, emtricitabine, and tenofovir) was added.

The treatment course was complicated by the development of immune reconstitution inflammatory syndrome (IRIS) reaction which was manifested by recurrent fevers, abdominal pain, respiratory failure and renal failure which necessitated discontinuation of the Atripla for about 2 months. The patient attributed these new symptoms to INH and was unwilling to take further INH. His antituberculosis regimen was changed to moxifloxacin, ethionamide, rifampin, ethambutol and PZA. Moxifloxacin and ethionamide were discontinued when drug susceptibility results became available.

After 3 months of treatment, a skin biopsy of a small thigh lesion revealed Kaposi sarcoma, while a cervical lymph node biopsy revealed necrotization with acid fast bacilli, but was culture negative. The patient subsequently received a further 9 months of therapy with daily rifampin, ethambutol and PZA. Treatment was self administered and the patient was confirmed to be adherent by pharmacy pill count and multiple physician visits. The patient tolerated the treatment well with significant clinical improvement. Sputum cultures converted to AFB negative by the third month. After 1 year of antituberculosis therapy, the pulmonary infiltrates had resolved and his CD4 count rose to > 400 cells.

Despite the good radiographic, bacteriologic, and clinical response to treatment, the patient had persistent lymphadenopathy. At the completion of 12 months of Rifampin, Ethambutol, and PZA, two tender, erythematous and fluctuant cervical nodes were still present. Aspiration of the larger node obtained about 1 cc of purulent fluid which was AFB smear positive and PCR positive for *M. tuberculosis*, but culture negative. Treatment was stopped and the patient remains asymptomatic. The lymph nodes have slowly regressed in size during the 3 months after discontinuation of antituberculosis treatment.

Treatment was extended to 12 months in this patient due to the slow conversion of sputum cultures to negative, disseminated disease and HIV infection, and the non standard treatment regimen.

PATHOPHYSIOLOGY

Mycobacterium tuberculosis is most commonly spread via the respiratory route by inhalation of infected aerosols. These aerosols contain small droplets, termed infectious droplet nuclei, which contain viable *M. tuberculosis* organisms. After inhalation of *M. tuberculosis* into the lungs, a short period of replication occurs prior to mobilization of a lymphocyte-mediated immune response. During this initial phase of infection, the tuberculosis bacilli disseminate to extrapulmonary sites via lymphohematogenous spread. This process results in the influx of lymphocytes and macrophages into infected lymph nodes producing granulomatous inflammatory responses and granuloma formation.

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EPIDEMIOLOGY

Ninety-five percent of mycobacterial cervical lymph node infections in adults are caused by *M.tuberculosis*. Tuberculous lymphadenitis accounts for 5% of all tuberculosis cases in the immunocompetent adult population and is the most commonly diagnosed form of extrapulmonary TB in the US and globally (5,8,19,22). In 2009, 44.9 % of all extrapulmonary TB cases in the United States were lymphatic (4). Cervical lymph node involvement, previously termed "scrofula", is the most common site. In a study of 100 adult immunocompetent patients with TB lymphadenitis, 92% had cervical or supraclavicular lymphadenitis (2).

CLINICAL PRESENTATION

In most cases tuberculous lymphadenopathy is associated with progressive primary tuberculosis. Patients note painless masses which are persistent and tend to enlarge. The infected lymph nodes are initially firm and have a rubbery consistency. They generally become firmer as the disease progresses. In the majority of cases there are no general or systemic symptoms, however malaise and weight loss have been noted in 20 - 43% of patients (10). Two thirds of patients present with multiple lymph nodes and one third have bilateral lymph node involvement. In some instances the nodes become fluctuant and may rupture resulting in a draining fistula or ulcer.

HIV infected patients usually present with systemic symptoms(malaise, weight loss fever). Initially the nodes of HIV infected patients tend to be firm, discrete and painless. If left unchecked the nodes become fluctuant and drain spontaneously with a sinus tract formation. According to a 1994 study conducted by the Tanzanian National Institute of Medical Research, which compared the clinical features of HIV seropositive and HIV seronegative patients with tuberculous lymphadenitis, the lymph nodes of HIV seropositive patients were significantly less enlarged than in HIV seronegative patients (1). Half of the HIV infected patients had lymph nodes smaller than 2.5 cm(1). According to a study conducted by the Bamrasnaradura Infectious Diseases Institute in Thailand Paradoxical re-enlargement of involved lymph nodes along with fever are also the most common clinical features of Immune reconstitution inflammatory syndrome(3).

DIAGNOSIS

Diagnosis can be made by a positive sputum culture for *M. tuberculosis* in a patient with pulmonary disease and enlarged nodes. When respiratory samples are smear and culture negative, either a fine needle aspiration (FNA) for cytology and culture or an excisional biopsy for smear, culture, and pathological examination should be done. The smear is often negative in tissue specimens due to the low number of organisms, but culture may be positive in up to 80 percent of persons. (24) The presence of non caseating granulomas in an individual with risk factors for tuberculosis, especially if the individual has a positive tuberculin skin test (Mantoux) and/or interferon gamma release assay (IGRAs), supports a clinical diagnosis of tuberculous lymphadenopathy. However the pathology alone does not differentiate tuberculous adenopathy from other granulomatous infections. Recently PCR has been used by some clinicians but results have been variable.

TREATMENT

Effective treatment of TB lymphadenopathy caused by drug susceptible *M. tuberculosis* can usually be accomplished with the 6 month standard short course therapy regimen. A 1986 study by the British Thoracic Society noted similar results when a 6 month regimen of INH and rifampin, supplemented by PZA was given compared to 9 months of INH and rifampin. Nine patients out of the initial 199 were diagnosed with clinical relapse but all 5 of the nine who had specimens cultured were negative (17). Paradoxical enlargement of involved lymph nodes or even the appearance of newly enlarged lymph nodes can occur while patients are receiving appropriate therapy. As occurred in the case described above, these paradoxical reactions rarely indicate treatment failure. However they often necessitate a repeat lymph node aspirate or biopsy to exclude disease progression or emergence of drug resistance. A report by the Lancashire Postgraduate School of Medicine and Health of the clinical outcomes of 100 cases of TB lymphadenitis studied prospectively in Preston, UK found; despite the paradoxical enlargement of lymph nodes during treatment, 6 month treatment is sufficient unless bacteriologically confirmed relapse occurs. Treatment, either surgical or medical, of residual lymph nodes at the end of therapy is not required unless the presence of viable TB bacilli is confirmed through culture.

TEACHING POINTS and KEY CONCEPTS

1. Lymph node disease is the most commonly diagnosed form of extrapulmonary TB.

2. The most common cause of cervical lymph node enlargement in developing countries is TB.

3. Six months is usually sufficient for the treatment of lymphatic TB unless there is drug resistance, bacteriologically confirmed delayed response, or treatment failure (positive culture at 4 months).

4. Treatment often needs to be extended in HIV infected individuals, especially in those with extensive or disseminated disease and in those with delayed sputum conversion (positive at two months of later).

5. A presumptive diagnosis of TB as the cause of enlarged lymph nodes is made when a positive culture for *M tuberculosis* is available from another site (usually respiratory). Patients without positive respiratory cultures should have either a FNA of the node for smear, culture, and cytology or an excisional biopsy for smear, culture, and pathological examination. Smears may be positive < 50% of the time but cultures are positive in up to 70% of individuals. A positive TST or IGRA may provide additional support for the diagnosis.

6. Lymphadenopathy as part of disseminated TB is much more prevalent in HIV infected patients.

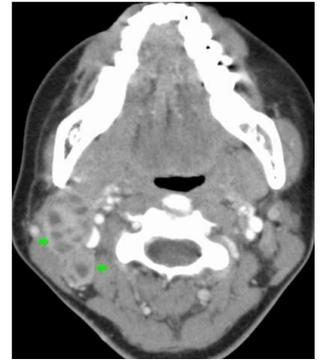
7. Up to 16% of patients develop new nodes during the course of TB Treatment. This represents an immune response to killed mycobacteria. Residual lymphadenopathy at the conclusion of treatment is present in 23-41% of patients and does not require extension of therapy unless the culture is positive.

8. The enlargement of additional nodes during treatment is a common symptom of an IRIS reaction. Lymph node re-enlargement and fever are the most common symptoms of an IRIS reaction.

9. Lymph node aspirates which are smear or PCR positive are not an indication of treatment failure. In this clinical situation, the positive smear or PCR is usually due to the presence of non-viable organisms. A positive culture is usually needed to document treatment failure

10. Surgical excision is rarely required as a treatment for tuberculosis cervical lymphadenopathy. This patient's biopsies were done to exclude treatment failure and other disease processes.

11. TB lymphadenopathy in HIV negative individuals is usually not associated with constitutional symptoms (fever, malaise, weight loss, night sweats), however systemic symptoms are common in HIV infected individuals.



*****Pictures are intended to show examples of TB lymph node disease, they are not related to this specific case presentation*****

REFERENCES:

1. Perenboom RM, Richter C, Swai ABM., Kitinya J, Mtoni I, Chande H, Kazema RR: Clinical features of HIV seropositive and HIV seronegative patients with tuberculous lymphadenitis in Dar es Salaam : *Tubercle and Lung Disease* (1995) 76, 401-406
2. Blaikley JF, Khalid S, Ormerod LP: Management of peripheral lymph node tuberculosis in routine practice: an unselected 10-year cohort. *INT J TUBERC LUNG DIS* 15(3): 375-378
3. Manosuthi W, Kiertiburanakul S, Phoorisri T, Sungkanuparph S: Immune reconstitution inflammatory syndrome of tuberculosis among HIV-infected patients receiving antituberculous and antiretroviral therapy. *Journal of Infection* (2006) 53, 357e363
4. CDC. Reported Tuberculosis in the United States, 2009. Atlanta, GA: U.S. Department of Health and Human Services, CDC, October 2010.
5. Thompson, M. M., Underwood, M. J., Sayers, R. D., Dookeran, K. A. and Bell, P. R. F. (1992), Peripheral tuberculous lymphadenopathy: A review of 67 cases. *British Journal of Surgery*, 79: 763-764. doi: 10.1002/bjs.1800790815
6. Dandapat, M. C., Mishra, B. M., Dash, S. P. and Kar, P. K. (1990), Peripheral lymph node tuberculosis: A review of 80 cases. *British Journal of Surgery*, 77: 911-912. doi: 10.1002/bjs.1800770823
7. Nayak, S., Mani, R., Kavatkar, A. N., Puranik, S. C. and Holla, V. V. (2003), Fine-needle aspiration cytology in lymphadenopathy of HIV-positive patients. *Diagnostic Cytopathology*, 29: 146-148. doi: 10.1002/dc.10340
8. Golden MP, Vikram RH, Extrapulmonary Tuberculosis: An Overview. *Am Fam Physician*. 2005 Nov 1;72(9):1761-1768.
9. Baran R, Tor M, Tahaoglu K, Ozvaran K, Kir A, Kizkin O, Turker H. Intrathoracic tuberculous lymphadenopathy: clinical and bronchoscopic features in 17 adults without parenchymal lesions. *Thorax* 1996;51:87-89
10. Schlossberg D, ed. Tuberculosis and Nontuberculous Mycobacterial Infections, Sixth Edition; 2011 May 10
11. Jha BC, et al. Cervical tuberculous lymphadenopathy: changing clinical pattern and concepts in management. *Postgrad Med J*. 2001;77(905):185-187. doi: 10.1136/pmj.77.905.185.
12. Bezabih, M., Mariam, D. and Selassie, S. (2002), Fine needle aspiration cytology of suspected tuberculous lymphadenitis. *Cytopathology*, 13: 284-290. doi: 10.1046/j.1365-2303.2002.00418.x
13. Mehta JB, Dutt A, Harvill L, Mathews KM . Epidemiology of extrapulmonary tuberculosis: a comparative analysis with pre-AIDS era. *Chest* 1991;99:1134-8
14. Kumarasamy, N., Chaguturu, S., Mayer, K. H., Solomon, S., Yepthomi, H. T., Balakrishnan, P., & Flanigan, T. P. (2004). Incidence of immune reconstitution syndrome in HIV/tuberculosis-coinfected patients after initiation of generic antiretroviral therapy in India. *Journal of Acquired Immune Deficiency Syndromes*, 37(5), 1574-1576.
15. Carter EJ, Mates S. Sudden enlargement of a deep cervical lymph node during and after treatment for pulmonary tuberculosis. *Chest* 1994;106:1896-8
16. Yuen PW, Wong SHW, Tam CM, Chan, SL, Wei WI, Lau SK, Prospective randomized study of thrice weekly six-month and nine-month chemotherapy for cervical tuberculous lymphadenopathy. *Otolaryngology - Head and Neck Surgery*, 1997, v. 116, p. 189-192

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REFERENCES:

17. Campbell IA, Ormerod LP, Friend AJ, Jenkins PA, Prescott RJ, Six months versus nine months chemotherapy for tuberculosis of lymph nodes: Preliminary Results. *Respiratory Medicine* 1992; 86, 15-19
18. Campbell IA, Ormerod LP, Friend AJ, Jenkins PA, Prescott RJ, Six months versus nine months chemotherapy for tuberculosis of lymph nodes: Final Results. *Respiratory Medicine* 1993; 87, 621-623
19. **Clevenbergh P, Maitrepierre I, Simoneau G, Raskine L, Magnier JD, Sanson-Le-Pors MJ, Bergmann JF, Sellier P**, Lymph node tuberculosis in patients from regions with varying burdens of tuberculosis and human immunodeficiency virus (HIV) infection. *Presse Med.* 2010; 39: e223-e230
20. Geldmacher H, Taube C, Kroeger C, Magnussen H, Kirsten DK. Assessment of lymph node tuberculosis in Northern Germany*: a clinical review. *Chest* 2002;121:1177-82.
21. Sarma PK, Chowhan AK, Agrawal V, Agarwal, Fine needle aspiration cytology in HIV-related lymphadenopathy: experience at a single centre in north India. DOI:10.1111/j.1365-2303.2009.00712.x
22. Rawat J, Sindhwani G, Dua R, Primary multi-drug resistant tubercular lymphadenitis in an HIV infected patient. *Indian J Tuberc.* 2009 Jul;56(3):157-9
23. Forget F, Challoner K, Scrofula: emergency department presentation and characteristics. *Int J Emerg Med* (2009) 2:205-209
24. Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J. (2005). *Harrison's principles of internal medicine* (16th ed.). New York: McGraw-Hill Medical Publishing Division.

TB LINKS

TB Education and Training Network

<http://www.cdc.gov/tb/education/Tbetn/default.htm>

Find TB Resources

www.findtbresources.org

Tuberculosis Epidemiologic Studies Consortium (TBESC)

<http://www.cdc.gov/tb/topic/research/TBESC/default.htm>

Regional Training and Medical Consultation Centers' TB Training and Education Products – (Joint RTMCC Products Page)

<https://sntc.medicine.ufl.edu/rmccproducts.aspx>

Program Collaboration and Service Integration (PCSI)

<http://www.cdc.gov/nchstp/programintegration/Default.htm>

****If your organization has any additional links for TB resources you would like published, please send them to Alysia.gibbons@uthct.edu****

