Submission to the all party Parliamentary Group on global Tuberculosis

From

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SUMMARY

Regarding DIAGNOSTICS IN TUBERCULOSIS

- A group of patients exist with clinical presentation compatible with tuberculosis, but negative tests for tuberculosis
    - According to World Health Organization guidelines these patients are labeled 'smear negative tuberculosis'

- Many of these patients do not respond to empirical tuberculosis treatment
    - This is often due to drug resistance, but would also occur if the diagnosis of tuberculosis was wrong

- Chronic Pulmonary Aspergillosis (CPA) is debilitating and ultimately fatal disease, which:-

    - Is a well-described complication of pulmonary tuberculosis.
    - Can result in near identical symptoms and chest x-ray changes as tuberculosis

- CPA can be diagnosed using *Aspergillus* IgG blood test, together with radiological changes and culture.
    - AT PRESENT CPA TESTING IS NOT ROUTINELY PERFORMED in patients with 'smear-negative tuberculosis'

- CPA can be treated effectively with oral and intravenous antifungal drugs and (in selected cases) surgery.
    - These treatments can be delivered in resource-poor settings
    - Although the oldest of these antifungals are available globally, they are not routinely prescribed at present

- Anti-tuberculous drugs lower oral antifungal drugs concentrations to zero, so distinguishing between the 2 diseases is critical.

- We submit that:
  - Up to 20% of those with suspected tuberculosis, will in fact be suffering from CPA
  - Patients being investigated for TB should be routinely screened for CPA using serum *Aspergillus I*gG as an initial screening test, with CT scan in patients with positive *Aspergillus I*gG results.
  - This is particularly important in patients who have a recurrence of symptoms after initial treatment of tuberculosis.

OVERVIEW

1 – The problem of 'smear-negative tuberculosis'

The World Health Organization recommends that all patients suspected of having tuberculosis be investigated with a sputum smear test. The sensitivity of these tests can be low, especially if patients are co-infected with HIV, as is often the case in Africa. More sensitive investigations such as culture, sputum PCR testing and biopsy are often not available for investigation of individual patients in resource poor settings. When patients are suspected of having tuberculosis, but smear test is negative the World Health Organization recommends treating for tuberculosis if the following criteria are met:-

1. Three sputum smear tests performed and are negative
2. Chest x-ray is abnormal
3. A course of antibiotics does not result in resolution of symptoms

These guidelines are implemented in most resource poor counties. They do not include specific investigations for other conditions, such as fungal lung disease that can mimic tuberculosis.

2 – Chronic pulmonary aspergillosis

The existence of fungal balls in lungs (aspergilloma) has been known about since the 18th century, but they had been regarded as a rare condition. Treatment was often considered unnecessary, but the affected area might be removed to prevent the risk of bleeding.

In 2003 our research group in Manchester (now the UK National Aspergillosis Centre) described a new disease entity termed Chronic Pulmonary Aspergillosis (1). Whereas fungal balls were previously considered to be largely asymptomatic, patients with this disease were often seriously unwell with cough, breathlessness, fatigue and ultimately suffered progressive lung destruction and life threatening haemoptysis (coughing up blood). Research groups in Senegal,

Ethiopia, France, India, Japan, China and Korea have now confirmed the existence of this disease in their countries (2–8). The 5 year mortality rate of CPA in Japan is 85% (6).

The disease is diagnosed when the following conditions are met (abbreviated);-

1 – Over 3 months symptoms (cough, haemoptysis, breathlessness or weight loss)
2 – Progressive cavitation OR fungal ball on chest x-ray
3 – Raised antibodies to *Aspergillus* on blood testing

It is important to note that fungal balls are only noted on CXR in a minority of these patients (1, 9) and that in most cases progressive cavitation is all that is noted. This can be identical to the appearance of tuberculosis. The symptoms can also be exactly the same as the symptoms of tuberculosis. The only criterion that clearly differentiates tuberculosis from CPA is blood testing for *Aspergillus* antibodies. This test is not routinely performed as part of tuberculosis investigations at present.

3 – The link between tuberculosis and TB

There is a clear link between the CPA and tuberculosis. Previously treated tuberculosis is a common underlying condition in patients treated for CPA at the UK National Aspergillosis Centre (10), even though tuberculosis is uncommon in the UK. Prior TB was the main risk factor for CPA in 75% of cases in India, 71% of cases in China and 93% of cases in Korea (7, 8, 11). Data from Africa is limited, but 100% of 24 African patients operated on for CPA in one series had treated tuberculosis (TB) as an underlying lung disease (2).

The risk of developing CPA after TB was described in a study published by the British Tuberculosis Association in 1968-70. The study prospectively examined 544 patients who were treated for TB and had cavities on chest–ray after treatment. Within three years, 34% of these patients had developed antibodies to *Aspergillus* and 63% of patients with antibodies developed an aspergilloma. 42% of those with aspergilloma then developed haemoptysis (12). This substantial survey shows that CPA is a common complication of tuberculosis and that it can lead to life threatening complications in just 2 years.

The UK National Aspergillosis Centre group recently led an effort to estimate the global prevalence of CPA secondary to tuberculosis. Calculations were performed based on the information above and published rates of lung cavitation after tuberculosis treatment in different counties around the world. The total global prevalence of CPA secondary to TB has estimated at between 0.8 and 1.37 million cases with 43 cases per 100,000 population predicted to occur in Congo and Nigeria (13). A recently revised estimate for India using the same modeling methodology indicated an annual incidence of CPA of 27,000-170,000 and a 5-

year prevalence of CPA of 290,147 cases (2.4 per 100,000) (Agarwal, Denning and Chakrabarti – manuscript submitted).

Put together these studies demonstrate that CPA a serious disease that is a fairly common complication of tuberculosis affecting a large number of people worldwide. It can be treated effectively with surgical removal of the affected area (2, 7). It can also be treated effectively with antifungal drugs - the efficacy of cheap, generic itraconazole given with limited monitoring was recently demonstrated in a randomized controlled trial in India (5).

The problem is that patients are not diagnosed with CPA, as *Aspergillus* antibody tests are not normally available in resource-poor settings where tuberculosis is common. Indeed it is not clear from multiple contacts that such tests are available anywhere in Africa.

4 – Diagnosing CPA in resource-poor settings

Patients with CPA are likely to present to tuberculosis services as the symptoms are almost identical to those of tuberculosis. CXR is routinely used in tuberculosis diagnostic programs throughout the world and that CT scan (to confirm the diagnosis and / or prepare for surgery) is available in most referral hospitals, especially those with cardiothoracic surgery where CPA could be treated surgically. The missing requirement is *Aspergillus* antibody testing

At the UK National Aspergillosis Centre testing for *Aspergillus* IgG (antibody) is provided using the ThermoFisher Scientific ImmunoCAP testing system. This system is fully automated and has proven efficacy for the diagnosis of CPA and monitoring response to treatment in CPA in published studies (9, 14). It has been shown to produce consistent results when used by different operators or in different laboratories (15, 16). The Seimens Immunolite is another fully automated testing system for *Aspergillus* IgG, which is manufactured in the UK and has been shown to have acceptable correlation with the ImmunoCAP system (16). Unfortunately while convenient and effective in a well-resourced setting both these systems require large, expensive machines that require frequent expert maintenance. As such they are not appropriate for large-scale use in resource poor settings.

Alternatives do, however exist. Manual *Aspergillus* IgG ELISA tests are manufactured by many companies, including Serion and IBL (Germany), Bio-Rad (France), Bordier (Switzerland), Bio-Enoche (China) and Omega (UK). Of these only Bio-Rad and Serion currently have published proof of performance in CPA diagnosis (14, 17). These tests all require a machine (spectrophotometer) to read the result. This will be available in the laboratories of major hospitals in resource poor settings as it is also needed to read some commonly used tests, such as those for HIV and hepatitis. They cost less than £12 per assay.

A purely manual test for *Aspergillus* IgG does exist, which is performed with a simple pipette and produces a result visible to the naked eye. It is a haemagglutination assay manufactured by ELITech diagnostics (France). 94 samples can be run as a screen for one kit costing £64 in the UK. A lateral flow device (the technology used in over-the-counter pregnancy tests) that detects an *Aspergillus* antigen has also recently been released by OLM (UK) after being developed at Exeter University. These tests would be ideally suited to use in resource poor settings, but their efficacy for use in the diagnosis of CPA is not yet proven.

6 – Ongoing Research

The UK National Aspergillosis Centre is currently undertaking a large survey in Uganda in collaboration with the University of Manchester and Gulu University. This will define the prevalence of CPA in patients previously treated for tuberculosis in that location. Initial data suggests the prevalence will be between 3% and 15%.

We are also undertaking a large comparison of testing methods for *Aspergillus* IgG. This will include validation of most of the assays listed earlier in patients with a clear diagnosis of CPA at the UK National Aspergillosis Centre and comparison of the efficacy of different tests for the diagnosis of CPA in patients in the Ugandan study.

These studies should be complete and published within the next 18 months. At this point we will be able to make a clear evidence-based recommendation as to the best method of testing for aspergillosis.

CONCLUSIONS

CPA is a frequent complication of tuberculosis. It is also likely to be a major differential diagnosis for any patient presenting with suspected tuberculosis in a high prevalence area. It is a severe condition causing disability and early death. It is treatable with relatively inexpensive antifungal drugs and surgery, yet at present it is almost never tested for in patients presenting with compatible symptoms.

We recommend that testing for CPA be performed in all patients presenting with suspected tuberculosis in whom smear tests for TB are negative. It may also be appropriate to screen patients who have completed treatment for TB to detect the complication of CPA before too much lung is destroyed. This should be done by the provision of *Aspergillus* IgG testing in addition to chest x-ray. Treatment with itraconazole (and surgery in selected cases) should then be made available to patients. The most convenient way to do this may be as an adjunct to existing tuberculosis control programs.

More detailed information is available online at:
http://www.life-worldwide.org/chronic-pulmonary-aspergillosis1/
http://www.gaffi.org/wp-content/uploads/Chronic-pulmonary-aspergillosis-Fact-Sheet.pdf

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