

Cavitating pulmonary tuberculosis: a global challenge

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Introduction

Tuberculosis (TB) remains a major challenge and burden on healthcare with devastating fallout. The World Health Organization (WHO) has declared it a 'global emergency'. In the next 20 years, with 200 million projected to develop the disease and 36 million expected to die,¹ it paints a bleak picture. In spite of several programmes by WHO, the relapse rate in cavitating disease remains high (21–25%)^{2,3} and 2–4% annual new cases are multiple drug resistant (MDR). Urgent action is needed.⁴

Why quantify the disease?

Risk and severity stratification for disease is now common place. Risk stratification helps formulate step care plans with intensification of treatment in severe disease. TB is rarely quantified radiologically at the time of its diagnosis or the extent of its resolution, residual lung damage or its effects recorded on completion of therapy. This has resulted in poor outcomes in severe disease. Pulmonary TB was initially divided into three grades by the US National Tuberculosis and Respiratory Disease Association in 1961: minimal, moderately advanced and far advanced disease.⁵ If a genuine headway with TB is to be made, the management of severe disease needs a new approach.

Cavitating disease

Cavitating disease occurs in 40–87% of pulmonary TB. Cavity formation resulting from liquefaction of caesium is considered central to its spread and persistence. Patients with cavity have a bacterial load of up to 10¹¹ bacilli/gram, making it highly contagious. The majority of relapses and treatment failures are cavitating disease.⁶ Most cases of MDR and almost all cases of extensively drug-resistant TB (XDR-TB) are cavitating disease.⁷ Semi-quantitative reading on Lowenstein–Jensen medium showed very high bacillary load, in the core necrotic and liquefied caseous zone within the cavity. In closed cavities, 80% had more than 200 colonies whereas only 22% of other lesions had an equivalent number.⁸

Three important elements occur in cavitating TB. First, the immunopathology of cavitating pulmonary TB because of the high bacillary load is inextricably linked with hyper-exaggerated response to the perceived threat from mycobacterium tuberculosis (MTB). It initially elicits a TH1 response. Once the bacil-

lary growth in a cavity has increased manifold, it activates the TH2 response, triggering a putative architectural distorting cascade with very little reversibility possible, even with treatment. Second, once MTB has achieved a load of a billion plus bacilli/gram a population gradually slows down its activity, finally becoming dormant, the root of the cause of persistence and relapse. This could possibly be validated using high through-put techniques, evaluating gene expression profiles from bacilli within cavities. Lastly, it is understood that at this load there is a real, though small, threat of emergence of resistant mutants and a substantially bigger threat of secondary resistance in chronic cavity, the holy grail of MDR and XDR-TB.⁹

Rationale for expansion

The major breakthrough in the treatment of TB came in 1944 with the discovery of streptomycin and para-aminosalicylic acid (PAS). In 1952, isoniazid was added to the two drug regimen and later ethambutol replaced PAS (which had unacceptable side effects). The introduction of rifampicin in 1970 and pyrazinamide in 1980, however, revolutionised the treatment. The four drug regimen was considered a highly effective combination with capability of killing bacilli completely, providing protection against relapse and resistance.¹⁰ It also became possible to reduce the duration of treatment to six months, with an impressive cure rate of 95%.¹⁰ With the changing face of acid fast bacilli (AFB) and its unholy alliance with HIV it was natural for this regimen, which remained in use for 30 years, to lose its effectiveness in severe disease without being enhanced with new drugs.

There have been many attempts to find novel agents active against semi-dormant and sporadically multiplying microbes. A search is underway for a vaccine that could substantially enhance the cellular immunity, like a modified vacinia virus antigen 85A expressing MTB and, more recently, a new protein called EspC (discovered through research at Imperial College London) that could be targeted for a TB vaccine. It could be years, however, before a vaccine can be commissioned as a standard preventive measure.

In moderately advanced disease, standard short course therapy remains suboptimal and falls short of achieving a complete cure both bacteriological and radiological. In cavitating disease, unless the treatment is expanded at the outset, it is an opportunity lost, for the architectural damage will take place with irreversible complications leading to end-stage lung disease 'malignant tuberculosis'.¹¹

Logically, if the bacilli can be killed rapidly and bacterial load in a cavity reduced quickly, all three mechanisms that have been described can be pre-empted, resulting in complete cure. It is in

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this context that recommendations of expanding short course treatment appear appropriate in the quest to improve the outcome of cavitating disease.

Sackett defined evidence-based medicine as the 'conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients...[it] means integrating clinical expertise with the best available evidence from systematic research'.¹² Assuming that an appropriate objective for performance of a regimen is 95%+ cure rate, steps that can be taken to 'shift the curve to the left' should be considered. Conceptually this might be accomplished by strengthening either the early bactericidal activity (EBA) or late sterilising effects (killing bacilli in diminished states of metabolism so that relapses do not occur after treatment is terminated) of the regimen.¹⁰ New second line anti-TB drugs fit into these criteria. Levofloxacin acts upstream to rifampicin by inhibiting DNA coiling, transcription and translation. It reduces the RNA replication of the bacilli, making it easier for rifampicin to effectively and rapidly destroy them, while amikacin inhibits the final pathway of protein synthesis by ribosome.¹⁰ The addition of these two new bactericidal drugs to the existing armamentarium makes this six-drug regimen the most powerful combination that can be evolved with an ability to accomplish not only the initial dramatic killing, but drastically reduce the chances of them becoming semi-dormant. This regimen appears to be highly promising as it produces rapid smear negativity with early closure of cavity, making a complete and sustainable cure a reality. The prospect of resistance in chronic cavity is also greatly reduced. The six-drug regimen carries with it a much desired advantage of not exceeding the duration of short course therapy to nine months as recommended by WHO in cavitating disease, and has a potential of becoming the benchmark for treating cavitating pulmonary TB.

Our clinical experience

In our study, the first of its kind, we expanded a short course with levofloxacin and amikacin, and have treated 60 new smear positive moderately advanced cavitating pulmonary TB patients. With extensive previous experience in retreatment category,¹³ uninterrupted and meticulously instituted quality drugs as directly observed therapy, we were able to eliminate any risks of resistance to the drugs used. We have not experienced any unacceptable or severe side effects. The safety profile of this regimen has been scrutinised by another independent study which will be published shortly. We have observed a complete bacteriological cure at three months and radiological cure at the end of six months in a significantly greater proportion of the patients put on expanded regimen compared with those on the standard. Almost complete resolution of cavities and reversible architectural changes have been seen in a significant number of patients in the experimental group.

Conclusion

There is an urgent need to devise new modalities of treatment which should address the ground realities in treating severe disease. The results of our study indicate that this strategy can bring a paradigm shift in managing pulmonary TB. It can become a defining moment in the history of this ancient disease transforming the lives of millions of young patients, drastically reducing the pool of persisters, recurrent relapse and end-stage lung disease.¹⁵ A cure, realistically, is not just achieving smear negativity but resolution of the disease radiologically, translating into the restoration of complete physical, mental and social wellbeing. Every case should be quantified at the outset and in moderately advanced cavitating disease; treatment expanded upfront for this can play a pre-eminent role in achieving a complete cure.

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