MANAGEMENT OF MULTIDRUG RESISTANT TUBERCULOSIS (MDR-TB): OVERCOMING CHALLENGES AND IMPROVING CLINICAL OUTCOME IN A POOR RESOURCE SETTING

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ABSTRACT

Tuberculosis (TB) is one of the world's deadliest communicable diseases. Drug resistant – TB (DR-TB) occur when resistance develop to one or more anti-TB drugs. The emergence of, and increasing cases of DR-TB are purely human factor and this poses a great danger to the global TB care and control. Current treatment regimens and modalities for treatment are quite far from satisfactory with problems arising from long duration of treatment and complications from drugs used in the treatment. These two factors make the control of MDR-TB difficult with a risk of increasing numbers of extended drug resistant TB (XDR-TB). The cost implication is also enormous, both human and material resources. MDR-TB cure and control is demanding, requiring quality treatment of drug susceptible TB, expansion of rapid testing to diagnose MDR-TB, access to quality care, infection control and political commitment. Therefore all stakeholders are encouraged to intensify effort in the prevention and management of drug susceptible TB to avoid a global time bomb of increasing drug resistant TB which is much more difficult to manage.

INTRODUCTION

Tuberculosis (TB) remains one of the world's deadliest communicable diseases. In 2013, an estimated 9.0 million people developed TB and 1.5 million people died from this disease; 360,000 of whom were HIV positive [1].

TB is present in all regions of the world and the Global Tuberculosis report 2014 includes data compiled from 202 countries and territories [1].

The emergence of drug resistant tuberculosis (DR-TB) is a major threat to Global TB care and control [1,2]. In 2013, the World Health Organization (WHO) estimated that 480,000 people developed multi drug resistant TB (MDR-TB) of which 210,000 died [1].

Drug resistant – TB occur when resistance develop to one or more anti- TB drugs. MDR-TB is a form of TB caused by mycobacterium tuberculosis stain resistant to at least rifampicin and isoniazid [3, 4]. Current treatment regimens for MDR-TB are far from satisfactory. These usually require at least twenty months of treatment with combination second line drugs that are more toxic and less effective than the drugs used to treat drug susceptible TB [3, 4]. Indications is high that newer regimen with newer drugs bedaquline and delamanid will reduce the duration of treatment to 9-12 months [5].

Globally 3.5% of new and 20.5% of previously treated TB cases was estimated to have had MDR-TB in 2013. This translates to an estimated 480,000 people having developed MDR-TB in 2013 [1].

Here in Nigeria, previous WHO estimated about 3,600 patients with MDR-TB in 2012 and 3,700 in 2013. The National Drug resistant TB prevalence survey report 2013 showed that about 2.9% of newly diagnosed TB cases have MDR-TB while 14.3% of those on retreatment have MDR-TB. The prevalence among those that are newly diagnosed and on retreatment is 4.8% [6,7].

The WHO 2018 Global TB report showed that Nigeria currently has estimated cases of 5400 MDR/RR TB patients with 4.3 % among new cases and 25% in previously treated/ relapsed cases [8].

The treatment outcome for patients started on MDR-TB regimen is poor. In the 2010 cohort of detected cases only 48% were successfully treated; as a result of frequency of death (15%) and loss to follow-up (28%) commonly associated with adverse drug reaction, among other factors [2,9]. In 2011, only five of the 27 high MDR-TB burden countries (Ethiopia, Kazakhstan, Viet Nam, Myanmar and Pakistan) achieved treatment success rate of $\geq 70\%$ [1].

Ninety-two countries have reported at least one case of extensively drug resistance TB (XDR-TB), a form of MDR-TB with additional resistance to fluoroquinolones and second line injectable drugs (amikacin, kanamycin or capreomycin). On average an estimated 9.6% of MDR-TB cases have XDR-TB. Treatment options for XDR-TB are even more limited and with lower cure rates compared to MDR-TB. In a set of 200, XDR-TB patients only 33% survived while 26% of the patients died [2,9].

The development of and increasing prevalence of drug resistant TB is purely human factor, ranging from the patient behavior to those involved in the health care sector. Multidrug – resistant TB (MDR-TB) is multifactorial and fuelled by improper treatment of patients, poor management of supply and quality drugs, and airborne transmission of bacteria in public places. Case management becomes difficult and the challenge is compounded by catastrophic economic and social costs that patients incur while seeking help and on treatment [10].

WHO have outlined five priority actions right from prevention to cure which are needed to address the current MDR-TB epidemic [1,11]. These include:

1. High-quality treatment of drug susceptible TB to prevent MDR-TB.
2. Expansion of rapid testing and detection of MDR-TB cases.
3. Immediate access to quality care.
4. Infection control strategies and
5. Increased political commitment, including adequate funding for current interventions as well as research to develop new diagnostics, drugs and treatment regimen [1,11].

High quality treatment of drug- susceptible TB should be pursued to prevent emergence of DR-TB [11,12]. All patients diagnosed of TB, especially those with open pulmonary TB should be put on treatment without further delay. Treatment should be monitored and directly observe therapy strictly adhered to. Periodic testing while the patient is on treatment should be done to ensure that sputum conversion has taken place [11,12]. At any stage when it is assessed that the patient is not making clinical progress, the patient should be re-evaluated and GeneXpert MTB/RIF conducted to see whether drug resistance has developed [13,14,15]. Efforts should be made to treat the patient in an accredited centre and drug administration ensured at right dosing and duration.

A large number of TB drugs are used outside National tuberculosis programmes (NTPs) and NTP affiliated facilities, notably in the private sector where prescription practices and treatment management is of very poor quality [10]. This is an important contributor to drug resistant TB development in many settings. Some countries have successfully restricted the use of first-line TB regimens to NTP affiliated facilities, which is an effective method to help keep drug-resistant TB prevalence low [10]. It is essential to regulate the availability of both first- and second-line TB medicines and restrict use to facilities where quality prescription and treatment management can be ensured. In particular banning over-the-counter sales of TB drugs should be strictly enforced. Public and private health providers should be linked to NTPs through public-private mix approaches and be made to adhere to international standards of programmatic management of drug-resistant TB (PMDT). In that way they can be allowed access to free quality-assured TB medicines upon adherence to national guidelines [10].

The diagnosis of MDR-TB is rapidly expanding. The successful rollout of new diagnostic method is ensuring that more TB cases are currently diagnosed and treated [1].

Laboratory confirmation of TB and drug resistance is key step to ensuring that individuals with signs and symptoms of TB are correctly diagnosed and treated. In 2013, 58% of the 4.9million PTB patients notified globally were bacteriologically confirmed via a WHO recommended test, including rapid tests such as Xpert MTB/RIF [1,13,16]. In late 2013, WHO expanded its recommendations on the use of Xpert MTB/RIF to include the diagnosis of TB in children and some forms of extra pulmonary TB [1,13].

By June 2014, 108 countries with access to Xpert MTB/RIF at concessional prices had started to use the technology, and more than one million test cartridges were being procured each quarter [1]. In Nigeria the Gene Xpert sites have increased to 390 as at 2018 and patients are accessing this test free of charge. In spite of this only about 34% of the machines are utilized and 26% of estimated cases are being diagnosed [7]. This is a worrisome situation and one wonders what the cause really is. It seems that either the health workers are not aware of the availability of this test or that the patients refuse to access it. If the former is the case then effort should be made to increase awareness among health workers so that more cases will be detected. If the later is the case, then there is more work for the health worker in terms of disseminating information and thus creating more awareness, mobilization, counseling and education of at-risk individuals to subject themselves for screening.

Immediate access to quality care is mandatory once a diagnosis of MDR-TB is made. In Nigeria and some other places the Gene Xpert alert has been designed to notify the stake holders of new diagnosis of MDR-TB [6]. There are so many challenges facing immediate access to quality care.

At diagnosis the patient may not be ready for treatment because preparation has to be made; more especially family issues need to be sorted out. Permission has to be obtained from job places or schools if the patient is going to be admitted to a facility. Sometimes the patient may be ready for admission but getting a bed space may be difficult because the patients are admitted and discharged as cohorts. This delay often contributes to further spread but most these delays can be overcome if the patient is enrolled for community treatment.

At the treatment centre, the patient has to be counseled on the treatment modalities because the duration of treatment is long, the pills are many and the patient will be on an injectable for duration of eight months. Providing quality care involves taking care of co-morbidities like co-infection with HIV/AIDS, diabetes, heart failures and correcting anemia where necessary[17,18]. Patients may have developed complications eg. Cor pulmonale or may have been non ambulant and develop deep venous thrombosis (DVT) or even pulmonary embolism (PE) during period of transportation to the treatment centre. Such patients need to be identified and given additional care; otherwise early death is inevitable in such group of patients.

Pill burden may be a problem for patients with co-morbidities for example patients with HIV/AIDS and these patients have to be counseled[17]. Drug-drug interactions may occur and if recognized early, measures can be put in place to ameliorate the patients suffering. This could be possible if pharmaco-vigilant documentations are kept. Proper assessment before initiating treatment will reveal the patients who may develop complications from second line medications. For example, patients who have been on treatment with loop diuretics (frusamide): those with cor pulmonale, HIV or diabetic patients with chronic kidney disease or patients with congestive heart failure are at risk of developing complication with aminoglycoside (amikacin or kanamycin) treatment[17,18]. Also patients who have previously been treated with streptomycin may also have the same problem. It is important to look out for patients who have been treated severally with quinine based regimen for complicated malaria as these patients may be prone to ototoxicity while on aminiglycosides. Baseline investigations and periodic monitoring of liver enzymes, serum urea and creatinine and audiometry will identify patients with liver diseases, renal insufficiency and hearing impairment and adjustments can then be made to their regimen[10,19]. Hearing aids can be provided for patients who require it before they develop permanent deafness.

Psychiatry assessment should be done on patients once signs and symptoms of personality or behavioral changes are noted[20].

Feeding and nutritional requirements should be optimal. In the course of treatment the patient's appetite will improve and the patient will require more food[21]. Weight gain with improved appetite is an indication that the patients clinical condition is improving. Therefore the patient's weight need to be monitored monthly and drug adjustments made with increase in weight. Infection control remains an important aspect of control of MDR-TB. Policies have to be put in place to make sure that further spread is checked. Equipment for control of infection needs to be available and handy.

At all times, especially during direct contact with the patient the health worker should use his respirator (N 95 masks) while the patient wears his face mask[10,22,23]. Once diagnosis is made counseling should be carried out, so that the patient will know how to prevent his neighbors and loved ones from getting the infection. Using face mask in the home and confining to one room will limit spread of infection in the home. People living with infected patients should use respirators (N 95 masks). Cough etiquette should be taught and maintained at all times[10,22,23,24].

An area that should be looked into is when an MDR-TB patient has to be transported to a treatment centre which is often times far from the patient's home. This patient often travels with a public transport which has many passengers on board. This is a big risk for the unsuspecting passengers. Something has to done urgently in this regard.

The other aspect of infection control is the facility. The protective mechanisms in the laboratory must be put in place. There should be adequate water supply and the taps and extractor fans must be functioning well. The consulting rooms and the patients' waiting rooms must be designed to allow good ventilation. During construction and renovations, the "Air Changes per Hour (ACH)" when measured must be seen to fit into WHO specification which is a minimum ventilation of 12 ACH for Airborne infection isolation rooms (AIIRs)[25,26].

Many centres have infection control units that are not functional or not functioning optimally. The infection control unit must be doing enough supervision and ensure that facilities run according to specifications. Once supervision is not enough or stop, the health worker is bound to forget even the rudimentary things especially when there is work pressure.

Health system strengthening is prerequisite for preventing development of drug- resistant TB and this is mainly the function of the government. Poorly functioning health systems contribute to poor TB diagnosis and treatment outcomes that may lead to the development and spread of drug resistant TB[10]. Fundamental aspects of a good health care system include: sufficient health financing and universal coverage; government stewardship and regulation; a well developed health-care infrastructure; well trained and motivated workforce; uninterrupted supply of good management medicines; diagnostics and other commodities; and well functioning health information system, including disease surveillance[10]. These challenges exist within many health systems but they are particularly pronounced in low- and middle- income countries of which our country is included. Health financing is a major setback for many poor countries including Nigeria.

The budget made for the health sector is hardly sufficient to run it with the result that many facilities run skeletal services or are forced to close down. In Nigeria, the State owned health institutions are mostly affected. The WHO TB Global report 2018 showed that the national (Nigeria) budget for 2017 was 409 million US Dollars with only 8% domestic funding, 16% international funding; leaving a huge gap of 76% unfunded [7].This affects overall management of TB including early case detection and treatment of both drug susceptible and drug resistant TB.

The health insurance scheme should be made accessible to health workers especially those who work in MDR-TB and highly infectious areas. The healthcare giver who runs a risk of contracting DR-TB is poorly remunerated without any form of insurance or security. The Physician who runs the MDR-TB facility gets monthly stipend of about twenty-five dollars per month. There is no research grant or provision for sponsorships locally or internationally for him.

Research on TB diagnostic technologies are under development, but the funding required to rapidly evaluating whether these tests are accurate and ready for implementation is far from adequate. About ten new anti-TB drugs are currently in the late phases of clinical development and in the last four years two new drugs – bedaquline and delamanid have been approved for the treatment of MDR-TB under specific conditions [1]. A series of new combination regimens are currently being tested and show encouraging prospects for treatment of both drug susceptible and drug resistant TB. There are currently 15 vaccine candidates in clinical trials [1].The low – income countries including Nigeria are encouraged to join in these research works and innovations to control the spread of MDR-TB infection in our environment.

In conclusion, the emergence of and increasing cases of DR-TB poses a great danger to the global TB care and control. Current treatment regimens and modalities for treatment are quite far from satisfactory with problems arising from long duration of treatment and complications from drugs used in the treatment. These two factors make the control of MDR-TB difficult with a risk of increasing numbers of extended drug resistant TB (XDR-TB). The cost implication is also enormous; including time, human and material resources. Therefore all stakeholders are encouraged to intensify effort in the management of drug susceptible TB to avoid a global time bomb of increasing drug resistant TB which is even much more difficult to manage.

CONFLICT OF INTEREST: NONE

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