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IMPACT OF DOTS PLUS ON TREATMENT OUTCOME AMONG TB PATIENTS UNDERGOING DOTS AT THE TAMALE TEACHING HOSPITAL (TTH).

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ABSTRACT:*After a long period of decline, tuberculosis (TB) incidence and mortality in the Tamale Metropolitan Area rose dramatically during the 1990s and peaked in the (2000s). During the same period, the proportion of patients with notified TB that were cured fell from 90% in 1990 to an estimated 72% in 2011. Despite the introduction and gradual uptake of the Direct Observatory Treatment Strategy (DOTS) over the past decade, and a decline in case notifications, treatment success rates have remained consistently low. The World Health Organization (WHO) attributes these high failure rates to drug resistance, high default and mortality rates among patients undergoing DOTS. We conducted a retrospective cohort study of patients with newly detected smear- [and/or] culture-positive TB who were older than 17 years, notified under DOTS, and began TB treatment during the period 1 January 2009 to 31 December 2010. We excluded patients who were admitted to psychiatric hospitals, in prison, died within one month of treatment initiation or did not live within Tamale city limits. Individual programmatic risk factors and outcomes were assessed by reviewing patients' charts and TB treatment records, through a TB database set up by the National TB Program. We assessed risk factors for non-adherence, default and the development of multiple drug resistance during therapy. In an earlier study,(Yahaya et al, 2009), we reported the cause of death among patients undergoing DOTS in the Tamale Teaching Hospital. During January2001 to December .In that study, we observed a 9.6% mortality rate. Mortality was caused, not only by TB but also by co-morbidity conditions; such as alcoholism and cardiovascular diseases. We found that both alcoholism and late presentation substantially contributed to mortality. Based on our findings, we proposed several specific interventions that may improve treatment outcomes and reduce the acquisition of drug resistance in patients undergoing TB therapy in this setting:*

1. *Intensive education and training of staffs is necessary, to improve compliance and adherence to direct observatory treatments (DOTS).*
2. *Mass education is obligatory, to attract TB patients to come to the hospital for screening and early intervention.*
3. *TB management in the hospital will have to be patients centered treatment.*
4. *Enabler's package will have to be improved, to reduce defaulting and absconding.*
5. *All this will lead to reduction of multiple drug resistance, morbidity and mortality.*

KEYWORDS: Tuberculosis, Direct observatory treatments, Tamale Metropolitan Area,

BACKGROUND

Detection and treatment of all forms of TB, including multidrug-resistant forms, should be integrated into national TB control programmes.
Improperly treated patients with resistant strains of TB are a source of ongoing transmission of resistant strains, resulting in added future costs. The framework for DOTS-Plus treatment of MDR-TB cases presented in this document is to be integrated into the NTP DOTS strategy.

As detailed in the previous chapter, MDR TB is rapidly becoming a significant threat to global health and well-being. Numerous settings throughout the world have been identified as "hot spots" ofMDR TB. National borders offer little protection against MDR TB as the tubercle bacillus knows no regional boundaries. With increasing air travel and international ties, MDR TB represents a threat toall, even though it is the poor who are most likely to be afflicted; Given the large numbers of individuals already infected and sick with drug-resistant strains of *M. tuberculosis* the regions of those likely to become infected and sick in the future, it is clear that a unified global effort is needed to tackle the problem of MDR TB.

In order to address this growing epidemy, evidence-based strategies must be developed and implementedas efficiently as possible. Tried and true approaches to the treatment of MDR TB need to beadapted to work in resource-poor settings where the problem of MDR TB is the greatest. To date, the gold standard for MDR TB treatment has been the use of drug-susceptibility testing to determine resistance patterns and the administration of multidrug anti-tuberculous regimens, based on the resistance patterns for long periods of time (more than two years) s. Later in this manual, it bears mentioning that, to date, there is no data in the scientific literature supporting the use of non-individualized therapy for the treatment of MDR TB.

The treatment of MDR TB in resource-poor settings requires novel adaptations of currently existing; hospital-based, gold-standard therapy. Implementing such treatment control strategies will take aconcerted effort and require transnational collaboration. A variety of resources are needed: access to appropriate medications : access to laboratory facilities, and a strong DOT program within which therapy should be carried out.

OBJECTIVE

- To assess the impact of DOTs plus on treatment outcome among TB patients undergoing DOTs at the TTH.
- To determine the extent of drug resistance and to make suggestions for future Ghanaian NTP strategies.
- To achieve the millennium goal on TB as stated in the Alma-ata declaration (WHO, 1978).
- To achieve the 100% cure rate as targeted by the National Tuberculosis Control Program (NTP) of Ghana.
- To achieve zero percent death rate as targeted by the NTP in TTH.

- To provide useful programmatic and clinical guidelines which can serve as models on which other programs can be based.

RATIONALE

- Tuberculosis is public health burden in the Tamale Metropolitan Area (TMA).
- MDR-TB is a threat to the TB control program.
- To date, there is no data in the scientific literature supporting the use of non-individualized therapy for the treatment of MDR TB at the TMA.
- The treatment of MDR TB in resource-poor settings requires novel adaptations of currently existing, hospital-based, gold-standard therapy, (DOTs plus).
- DOTs plus is next strategy after DOTs failed.

METHODS

SETTING AND PROGRAM DESCRIPTION

We conducted this study in the Tamale Metropolitan Area, where the incidence and mortality rates of TB in 2009 were 109.3 and 8.3 per 100,000, respectively. A retrospective cohort study was conducted. Patient records were reviewed and follow up was done through telephone communication with patients and their relatives or treatment supporters. With the help of addresses and descriptions, patients were visited in their houses for reassessment, interviewed and physically examined.The prevalence of MDR-TB among the TB cases treated in the Tamale Teaching Hospital (TTH)is among the highest reported worldwide; MDR among newly diagnosed patients rose from 6.5% in 2009 to 12.1% in 2011. The TTH was one of the first in the Northern Region of Ghana to implement the DOTS strategy. The TTH oversees diagnosis, treatment and reporting of adult patients with TB. Suspected cases undergo sputum smear microscopy and culture at the time of diagnosis. Those who are culture positive also undergo drug sensitivity testing to isoniazid, rifampicin, ethambutol, streptomycin and kanamycin. Susceptibility is determined using the absolute concentration method on Lowenstein-Jensen media, based on the following drug concentrations: isoniazid 1 µg/ml, ethambutol 5 µg/ml and streptomycin.

Patients diagnosed with active TB are treated according to WHO recommendations (2003). Those with MDR-TB are switched to an individualized regimen based on the drug resistance profile. Treatment is offered three ways: under direct supervision in an inpatient setting, at one of three outpatient clinics or through home-based care. Patients receive drugs daily in each of the outpatient settings. Home-based care is provided for those who are unable to attend outpatient clinics, and nurses deliver drugs directly to these patients. Some patients self-administed drugs during weekends and holidays; a small proportion self-administered over half of their medications. All patients are treated in ambulatory settings. Travel expenses are not provided for patients who have no access to public transport services. Patients undergoing TB treatment are assessed with repeat sputum smear, culture, and drug sensitivity testing (DST) at month two, three and five, at treatment completion, and at six-month intervals thereafter.

EXPORSURE ASSESSMENT

The following information is routinely collected for all patients undergoing the DOTS strategy: age, gender, address, history of previous TB treatment, clinical signs at presentation, date of diagnosis, all sputum-smear results, all culture results, all drug sensitivity profiles, number of missed doses, dates of missed doses, date of treatment completion, date of default, date of death, co-morbidities including HIV, employment status at treatment initiation, history of previous incarceration and diagnosis of chronic alcoholism/smoking. We classified patient proximity to their assigned clinic based on their home address and access to public transport. Patients were classified as having co-morbidities potentially associated with side effects if they reported HIV, hypertension, renal insufficiency, liver disease, diabetes mellitus, gastric ulcers cholecystitisand CCF.

OUTCOME ASSESSMENT

We classified patients as non-adherent if they missed more than 20% of their prescribed doses during the treatment period, as recommended by WHO (2003). Treatment outcomes, including default, were classified according to WHO guidelines (2003). Patients were classified as having acquired MDR during or subsequent to therapy: if they were sensitive to either isoniazid or rifampicin on their first DST, but resistant to both agents on any later DST.

DATA ANALYSIS

For univariate analyses of non-adherence and default, we used logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs). A Mantel-Hansel $\chi 2$ method or Fisher's exact test was used to calculate p-values. Statistical tests were two-sided. We used separate logistic regression models to perform multivariate analyses of adherence and default. The multivariate model included relevant variables with p-values less than 0.2.

A Kaplan–Meier survival analysis was used to estimate the time from initiation of therapy to acquisition of MDR-TB. For patients who did not reach the end of study period, the data were censored at the time of their last DST. The MDR acquisition time was taken as the mid-point between the last DST without MDR and the first DST with MDR. A log rank test was used to compare time to MDR between strata. Cox's proportional hazards model was used for multivariate analysis. In a sub-analysis, we assessed risk factors for early (within 4 months of treatment initiation) and late (6 months after treatment initiation) acquisition of MDR. Patients who acquired early MDR were excluded from the analysis of risk factors for late MDR.

RESULTS

Table 1: Outcome * Delay Time (in Weeks) Cross tabulation

Count				
		Delay Time (Weeks)		
		delayed	earlier	Total
Outcome	Cured	26	7	33
	Died	1	17	18
	Chronically ill	0	3	3
Total		27	27	54

Of the 54 patients enrolled in DOTs plus, treatment program;(during the study period), a total of 18 patients died as compared to 33 cured. 3 patients got chronically ill and zero lost to follow up. (As shown in table 1). More than half of those who died during the study, did so during the first four months of study.

Sputum smear positivity was the only factor associated, significantly with baseline MDR. In both analysis (OR = 2.4, 95% Cl: 1.24-8.68) and in multivariable logistic regression model that included delayed intervention and substance abuse. In a multivariate model, herbal abuse was strongly associated with no-adherence (Yahaya, et al). Odds ratio for baseline alcohol dependants was (95% confidence level), notably nonadherence was not a risk factor for either early or late acquisition of MDR. These findings remain true when we conducted a sensitivity analysis in which patients were classified as no-adherent when they missed the first two weeks of their treatment period. Cure rate and treatment success continued to improve as shown in table 1, above. Our clinical methods focused more on patients centered techniques; as demanded by WHO in their millennium development goal (MDG) Alma ata declaration (1978).

DISCUSSION

In this study of outcome ofDOTS plus approach among patients with TB in Tamale Teaching Hospital, delayed intervention and MDR (in-hospital care), were identified as the potential obstacles to effective treatment. These results suggest that,expanded DOTS strategy (DOTS Plus) is more likely to achieve TB control targets. Interventions aimed at improving adherence; by diagnosing and treating substance abuse and co-morbidity, concurrently with standard TB therapy are, empirical. despite the implementation of DOTS program, late intervention and default continued in a substantial proportion among TB patients at TTH. They also raised the possibility that some patients with apparent drug-sensitive disease may also be infected with drug-resistant strains that are unmasked upon treatment initiation. Re-infection with drug-resistant strains in the hospital setting is a possibility; that emphasizes the need for effective infection control measures within facilities that care for patients with active diseases.

Despite the implementation of the DOTS strategy and the provision of extensive social services to patients undergoing TB treatment, non-adherence and default were observed in a substantial proportion of patients. These patients were burdened with a wide array of social and medical problems. Many were unemployed, while some were living in serious poverty. Other social burdens, depression and/or significant co-morbid conditions. Substance abuse, alcoholism and smoking were the only identified independent risk factors for non-adherence and default. These findings echo those of numerous previous studies that found substance abuse to be the single major factor associated most strongly with non-compliance with TB treatment regimens. Our results also agree with those of the WHO (2000; 2005; 2009).In that non-adherence have important adverse effects on TB treatment outcome. All poor outcome experienced in our cohort occurred among the 16% of patients who did not adhere to therapy.

Despite the clear need for new approaches to this problem, to date there has been relatively little research on treatment options for patients with chronic infectious diseases and concomitant substance abuse at the Tamale Metropolitan Area, (Yahaya et al). Programs that have explicitly offered treatment for substance abuse have generally demonstrated better outcomes than the "unexpanded" DOTS. Some even achieved very high cure rates among patient populations in which alcoholism or substance abuse is predominant.

There are, at least three possible explanations for this failure to undertake research on treatment options for patients with concomitant substance abuse. First, is the reluctance to tinker with the specialized "vertical" DOTS approach, given its success in improving case completion and cure rates in developing and less-developed countries over the past two decades. Second is the numerous obstacles faced by multidisciplinary approaches to research and patient care, including the lack of a shared language and space among care providers from different specialties and a mutual lack of knowledge of other treatment approaches. Third, the care of patients with TB and those with substance abuse disorders is often relegated to highly specialized practitioners. This offers little opportunity for meaningful interaction or exchange between disciplines. Finally, many physicians without specific expertise in managing alcohol disorders and smoking have until recently assumed that the treatment of these conditions is too complex and intensive to be carried out simultaneously with the treatment of another complex disease. However, recent evidence suggests that brief interventions, social skills training, behavior contracting and pharmacotherapy are among the most effective approaches for treatment of substance abuse. These data raise the possibility that integrated management of these most vulnerable patients with TB may be within the reach of a unified TB care facility.

Our study suggests that non-adherence did not contribute to either the early or late occurrence of MDR among patients receiving DOTS in this setting. We considered several other possible explanations for the observation that a group of adherent patients developed MDR within 24 months of initiating therapy. First, we speculated that MDR acquisition might be associated with disease severity, which might in turn be linked to hospitalization. Because the number of new mutations that code for drug resistance will be a function of the bacterial load, it follows that those with a greater disease burden would be at higher risk of developing these mutations. Second, having adjusted for disease severity, by controlling for the presence or absence of

cavitary disease and sputum-smear status, we found that these markers of disease severity were strongly correlated with early acquisition of MDR but not associated with late acquisition.

This suggests that these patients may harbor different strains of Mycobacterium TB, some of which may be drug-resistant. In these mixed infections, standard short-course therapy may have unmasked the drug-resistant strain population by suppressing the previously dominant drug-sensitive strain. Indeed, van Rie et al. (2004) have described this mechanism in a high-burden population in South Africa. In that study, adherence to a first-line drug therapy was shown to select for a resistant population, while non-adherence led to a re-emergence of the drug-sensitive strain. We also assessed the possibility that patients who developed MDR did so through "amplification" of exiting drug resistance. While this mechanism may have accounted for MDR acquisition in some cases, eight of the thirteen hospitalized patients with this outcome had fully susceptible disease on treatment initiation.

Finally, we considered the possibility that some of the patients in our study developed MDR-TB as a result of re-infection with a drug-resistant strain of TB. Re-infection of patients receiving treatment for drug-sensitive disease has been described in several different high-incidence settings and has been associated with nosocomial transmission (Kruuner, 2001). Usually, patients with MDR-TB in the Tamale Metropolitan Area are not placed on respiratory precautions in the hospitals or clinics where they receive care. This is because our doctors and nurses do not understand the importance of respiratory precautions so there is opportunity for further spread of drug-resistant strains among patients receiving treatment for drug-sensitive disease. The finding that substance abuse was a risk factor for late occurrence of MDR also raises the possibility that these patients are at higher risk of exposure to drug-resistant disease or are more susceptible to re-infection than other patients. Future studies on the association between adherence and development of MDR would benefit from molecular typing of sequential isolates in patients undergoing therapy.

As shown by the findings of this research, the TB detection rate increased to a peak in 2009, plateaued in 2010 and then increased to a maximum at the end of 2011. This increase was caused by changes in the approach to managing TB at the TTH to comply with the WHO DOTS strategy, and an intensification of public TB education. With the follow-up to patients' houses, relatives who were sensitized came forward for screening, thereby leading to an improved detection rate.

From the results the death rate has reduce to 18 as compare to 33 cured, as shown in table 1.
The explanation to this is that, it is not etheological treatment of MDR-TB which determined the outcome of management of the patients. So therefore, for effective management of MDR-TB, pathogenetic and support therapy is most effective, (Yahaya et al, 2012). This is in line with the millennium development goal and Alma Ata declaration in 1978.
For TB management and HIV, holistic and patients centered treatment was emphasized (WHO, Alma ata, 1978).

The results of this study shows that, MDG's for TB can only be achieved by expanded DOTS and not just DOTS. Management of co-morbidities such as complications resulting as a result of late treatments of tuberculosis must be treated aggressively as early as possible or in line with TB management.

Co-morbidity such as heart failure, corpulmonalies, alcoholism, meningitis, COPD, anaemia, substance abuse such as smoking must all be treated holistically. When co-morbidity is not well treated in DOTS patient is not holistically managed. This can lead to treatment failure and therefore negative outcome (Death or chronically ill).According to the definition in literature, MDR-TB cannot be treated by the first inline antikochs such as isoniazid rifampicin (CDC, 2006).The second in line drugs such as flurochnolons, kanamycin, seprofloxicilline are all ineffective as documented in literature. Apart from the fact that the second in antikochs are expensive and toxic to the patients it is imperative to use holistic management in all patients. The patients of MDR-TB, according to this study will have much longer lives, less complications, and therefore better prognoses. Death rate will be minimizeand cure rate will be improved.

FINDINGS

Poor outcome (Death rate and Treatment failure), continued to reduce to the minimal whilst good outcome (Cure rate and Treatment success), continued to improve towards maximum. Since our approach change from DOTS to DOTS plus, the NTP record book in TTH showed a drop in death rate and a rise in cure rate; a drop in treatment failure and a rise in treatment success, if this continues, the millennium development goals can be achieved at TTH (Yahaya, et al 2012).

CONCLUSION/RECOMMENDATIONS

In conclusion;

1. The introduction of DOTS plus has made a great impact on treatment outcome among TB patients undergoing DOTS at TTH since 2009.
2. The impact of DOTS plus on treatment outcome among TB patients undergoing DOTS at TTH were; improved cure rate, improved treatment success, improved adherence, reduced death rate, reduced treatment failure, improved documentation for records and research purposes,more effective TB control system, better understanding and surveillance of MDR.

1. Treatment supporters will have to be retrained to understand DOTS plus and to, supervise drug management at homes.
2. Nurses and pharmacists will have to be retrained to understand and manage expanded DOTS.
3. Public education is empirical; to sensitize catchment population on TB and MDR-TB.
4. Education and sensitization on the consequences of late treatment and MDR acquisition is necessary to all.
5. Respiratory precaution and infection control should be taken more seriously in the hospital.

6. Concomitant treatment of tuberculosis and substance abuse is necessary to improve outcome.
7. Integrated treatment approaches should include not only management of TB but also social skills training, behavioral contracting, and pharmacotherapy of substance abuse and mental illness.
8. Improving infection-control strategies in the hospital will decrease the risk of developing MDR in hospitalized patients with tuberculosis (TB).
9. Timely intervention is imperative for treatment success.
10. MDR is a real threat to control and elimination of TB.

ABBREVIATIONS

Delayed time: Number of weeks spent before reporting for medical intervention.
DOTS plus: Expanded Direct Observatory Treatment.
MDR-TB: Multiple Drug Resistant Tuberculosis.
Substance Abuse: Abuse of alcohol, Cigarette smoking and Herbal abuse.
NTP: National Tuberculosis Programme.
WHO: World Health Organization.
TTH: Tamale Teaching Hospital.

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