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Epidemiological Study of MDR-TB in Lebanon from 2005 to 2014

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ABSTRACT

Tuberculosis (TB), a common infectious disease, is a major public health problem especially with increased resistance to conventional treatment. Multidrug-Resistant Tuberculosis (MDR-TB) is difficult to cure, needs prolonged and expensive treatment, and has high morbidity and mortality rates. To determine the epidemiological status of MDR-TB in Lebanon, the data of all MDR-TB patients in Lebanon from 2005 to 2014 has been collected in a retrospective descriptive study at Azounieh sanatorium and Quarantine TB center and analyzed. The results focused on the incidence, the resistance pattern, the treatment and its outcome. The study showed 56 cases notified in Lebanon since 2005, about 1/3 were foreigners, increasing in incidence in the last 3 years, with male and young age predominance, highest numbers in Mount Lebanon. One-third of patients had the primary disease, most of them concentrated between 2013 and 2014. During the study period, no drug susceptibility tests (DST) for second-line drugs exist existed in Lebanon, so XDR TB cases were difficult to diagnose. Lebanon is classified as a low burden country for MDR-TB but the incidence is increasing lately mainly among foreign workers.

INTRODUCTION:

At no time in recent history, has TB been a great concern as it is today? The infectious microorganism, Mycobacterium tuberculosis, which is spread almost exclusively by airborne transmission, causes TB. The disease mostly affects the lungs but also involve any site in the body. When patients with pulmonary TB cough, they produce tiny droplet nuclei that contain the bacteria, which can be transmitted to others. A person, who becomes infected with TB, remains infected for years. A healthy immune system does not become ill but is usually not able to eliminate the infection without medications. This condition is referred to as "Latent Tuberculosis infection." Patients with the latter infection are asymptomatic and cannot spread the disease. About 10% of non- Human Immunodeficiency Virus (HIV) associated- Latent Tuberculosis infection will become ill with active TB at some time during their lives. Treatment of active TB involves taking multiple anti-TB drugs for at least 6 months.

If the patient does not take the medications regularly and for the full treatment period, the disease may not be cured and may recur with resistance. This, lead us to the recent outbreaks of MDR-TB posing an urgent public health problem. Resistance can be acquired through different molecular mechanisms and can be primary or secondary to a previous anti-TB treatment. Essentially, drug resistance arises in areas with weak TB control programs, areas classified by World Health Organization (WHO) as “High Burden Countries” (HBC) for MDR-TB. There are 27 HBC for MDR-TB. In these countries, at least 4,000 cases of MDR-TB are diagnosed each year, and/or at least 10% of newly registered TB cases are of MDR-TB (1). Directly Observed Therapy (DOT) is the best way of ensuring patient control. Another major control intervention is to detect and preventively treat persons who have latent tuberculosis infection that may be at high risk of developing the active form [2]. MDR-TB diagnosis and treatment are complicated but are improving nowadays through the innovational techniques, the newest drugs and the WHO and political efforts. The treatment is highly expensive, requires patients adherence, with common side effects. Lebanon is at risk for increasing MDR TB mainly due to its geographic location and the frequent immigrations from different endemic areas recently. Only two epidemiological studies were done on MDR-TB patients in Lebanon, but no publications in the last 10 years. This study cover MDR TB cases treated since the introduction of 2nd line TB drugs in Lebanon in 2005 and will describe the epidemiology and outcome of treatment.

TB control in Lebanon: In 1906, was the first Lebanese society for anti-TB. On 1908, first sanatorium, Maameltine, transferred after to Hemline. On 1914 second sanatorium appeared, Bhanness. On 1918 third sanatorium developed, Dahr el Bachek. On 1923 fourth sanatorium issued, Maameltine, the Armenian sanatorium which later on transferred on 1938 to Azounieh MDR-TB sanatorium. On 1950 first anti-TB center in Lebanon was opened, Quarantine. There are 8 TB public control centers, 2 at the central level in Beirut, 6 at the provincial level. The private sector refers 80% of total TB cases of the national TB programs. TB and DOTS strategy: First launch of DOTS was in 1998 with the help and collaboration of WHO, GLC, and IDA. On 2005 second, line drugs became available in Lebanon.

National Epidemiology: Two recent national studies: The first study: 84 samples of new pulmonary TB cases with three samples of patients previously diagnosed and under treatment, were collected between April 2004 and October 2005 from all Lebanese provinces. Resistance pattern: The isolates included 21 resistant cases (24.1%) (18 primary + 3 previously treated) in Beirut 15% (3/20) versus outside Beirut 27% (18/67) (OR= 0.48, 95% CI: 0.126–1.82, P = 0.085). They found single-resistant 4.6%; double-resistant 12.6%; triple-resistant 4.6%; quadruple-resistant 2.3%. Three of the MDR cases were the previously treated patients (3.5%) [3], the resistance pattern was: R 42.9% - H 81.0% - E 19.1% - S 76.2%. All MDR cases, except for one, were males, resulting in an M: F ratio of 7.0 (7/1) (OR = 3.1, 95% CI: 1.27–7.39, P= 0.3). All cases of MDR were concentrated within patient's aged 40–69 years.75% > 50 years. (Versus TB patients: 72% < 50 years and 7% are aged 20 or less). Most forms of resistance to drugs (79%) involved Isoniazid and Streptomycin, 17 resistance patterns were observed more than once. 9/17 came from the same regions [4]. The second study: Published in 2006, is conducted by Dr. M. Saade between July 2002 and April 2004, comparing the Prevalence of primary versus secondary MDR-TB in Lebanon. The study, which included 190 newly diagnosed tuberculosis patients, had found that 1% had the primary MDR-TB infection (0.66% Lebanese vs. 2.5% non-Lebanese). DST did on another 21 previously treated TB patients showed: 5 cases with no growth, 4 cases sensitive to all 1st line Anti-TB drugs (3 Lebanese versus 1 non-Lebanese), 1 patient mono-resistant to Isoniazid and 11 patients MDR (6 Lebanese versus 5 non-Lebanese) [5]. Concerning the MDR-TB notifications by WHO (Table 1) [6].

Table 1: MDR-TB notifications by WHO in Lebanon 2005-2013

	YEAR	TOTAL CONFIRMED CASES[a] OF RR-/MDR-TB	TOTAL CONFIRMED CASES[a] OF MDR-TB	ESTIMATED CASES OF MDR-TB AMONG NOTIFIED	
Lebanon	2005	3	3		
	2006	4	4		
	2007	2	2		
	2008	3	3		
	2009	5	4		
	2010	7	7		
	2011	3	3		
	2012	7	6		
	2013	10	9	7	(0–13)

Treatment costs in Lebanon: 100$ per sensitive TB patient and 2500-4000$ per MDR TB patient.

Objectives:

The recent demographic changes in the Middle East region, the numerous wars in the Arabic area especially the Syrian civil war, and the increasing number of foreigners' employee, have put our country at high risk for MDR-TB infection. On the other hand, MDR-TB in Lebanon has not been evaluated since 2005. Then we decided to conduct a study of all MDR-TB cases in Lebanon from 2005 till 2014 at Azounieh sanatorium and Quarantine TB center. Study objectives include: 1) - The incidence of the disease and its changes through a decade in parallel to the socioeconomic changes. 2) - The distribution of patients based on age, gender, weight, living area, compared with the older national studies. 3) - The resistance pattern of isolates. 4) - A comparison between Lebanese and non-Lebanese population and the effect of foreigners on MDR-TB epidemiology and 5) - The treatment outcome and its side effects in comparison with the international epidemiological studies.

MATERIALS AND METHODS:

Study subjects: A questionnaire completed by our team allowing collection of all MDR-TB patients data in Lebanon between January 1, 2005 and December 31, 2014. Information included demographic data, comorbidities, TB classification and resistance pattern, treatment,

adverse effects, microbiological and treatment outcome. Patient's names remained anonymous.

Exclusion Criteria's:

Patients diagnosed with MDR-TB but with no documented DST result. Patients who didn't receive treatment were included in the general incidence of the disease but were excluded from the further statistical analysis.

Inclusion Criteria's:

Patients had documented MDR TB infection, which had received or still on anti-tuberculosis therapy, in Lebanon between 2005 and 2014.

Methods:

Patient's data was gathered from Quarantine TB center and Azounieh sanatorium using a questionnaire (Appendix 1). Patients contacts (example: phone numbers) were available in case of lacking information.

Appendix 1: Questionnaire Form

Item 1) Patient's Initials: _____

Item 2) Gender: Female Male

Item 3) Date of Birth: _____

Item 4) Social History:

Nationality: _____ Residency_____

Item 5) Patient's Weight:_____

Item 6) TB classification:

Pulmonary Extra-pulmonary

Item 7) HIV status Positive Negative

Item 8) Registration group:

New Previously treated Failure

Item 9) Risk Factors:

Diabetes Renal disease Drugs Hematologic neoplasm

Head and neck cancer steroids >1m Transplant Cirrhosis Gastric

surgery Celiac disease others

Item 10) Date of sample taken for DST: ----------

Item 11) Result of DST: R versus S H R S E FQ

Item 12) Date of initial treatment: ----------

Item 13) Date of initiation of second line regimen treatment ----------

Item 14) Second line TB drugs received ----------

Item 15) Outcome of treatment:

Cure Death Complete still on treatment lost to follow up
Left the country

If death, causes: TB non TB

Item 16) Side effects experienced during treatment: Yes No

If yes specify:

- Arthralgia

- Myalgia

- Headache

-Gastrointestinal (Nausea, Anorexia, Diarrhea, Vomiting, Abdominal pain,

Epigastric pain)

- Neuropathy

Exclusion	Year	Gender	Registration Group	Nationality	DST	Outcome	Causes of Exclusion
Case 1	2013	Female	Pulmonary	Ethiopian	Sensitive to E Only	Left the Country	No Treatment
Case 2	2010	Female	Pulmonary	Lebanese	Sensitive to S Only	Loss of Follow up	No Treatment
Case 3	2008	Female	Lymphadenitis	Palestinian	No DST	Left the Country	No DST
Case 4	2007	Female	Pulmonary	Russian	Resistant to All	Left the Country	No Treatment
Case 5	2006	Female	Pulmonary	Syrian	Resistant to All	Left the Country	No Treatment

- Liver failure

- Hearing problem

- Psychiatric

- Severe allergy

Item 17) Month of conversion of smear and culture ----------

Item 18) Results: + or -

Month 0: smear culture GeneXpert

Month 1: smear culture GeneXpert

Month 2:

Data was uploaded to Excel sheet and statistical analysis was done by SPSS v16.

RESULTS:

Between 2005 and 2014, 56 patients had the MDR-TB infection based on Azounieh sanatorium and Quarantine TB center Data. Five out of these 56 patients were excluded from the study but were included in the general incidence number (Table 2).

General Epidemiology:

While the Lebanese population has changed in size from 3.8 to 4.1 million in the previous years and up to 5.8 million in 2014 [43], data showed that sensitive TB population has

increase in number from 391 cases in 2005 to 499 in 2011 then up to 730 cases in 2014 (despite a previous continuous decrease between 1999 and 2005), whereas the distribution of MDR-TB cases over years showed the highest numbers in the last 3 years (2012, 2013, 2014 respectively) accounting alone for 22 cases (43%) (Figures 1, 2), MDR-TB to sensitive-TB ratio throughout the last decade were the highest in 2005 2%, and the lowest in 2008 0.3% with a mean ratio of 0.95%. Concerning the nationality, 36 were Lebanese vs. 15(29.41%) foreigners: 5 Palestinians, 5 Syrians, 3 from Ethiopia, 1 from Angola and 1 from Russia. 9/15 (60%) of the foreigners and all 5 Syrian MDR-TB patients were diagnosed between 2012 and 2014.

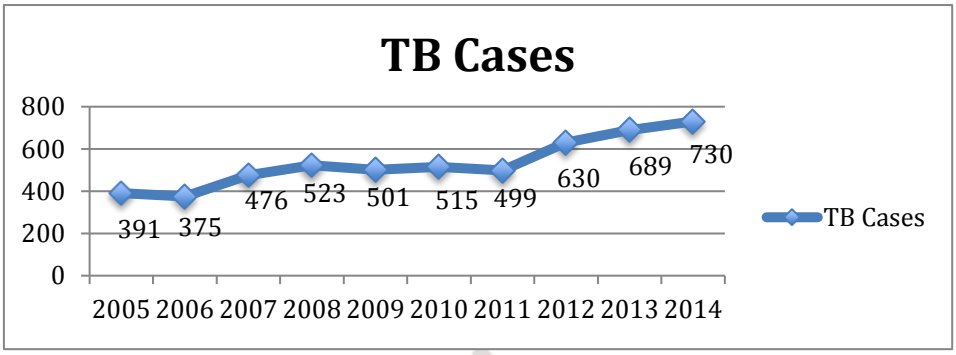

Figure 1: TB Cases in Lebanon 2005-2014

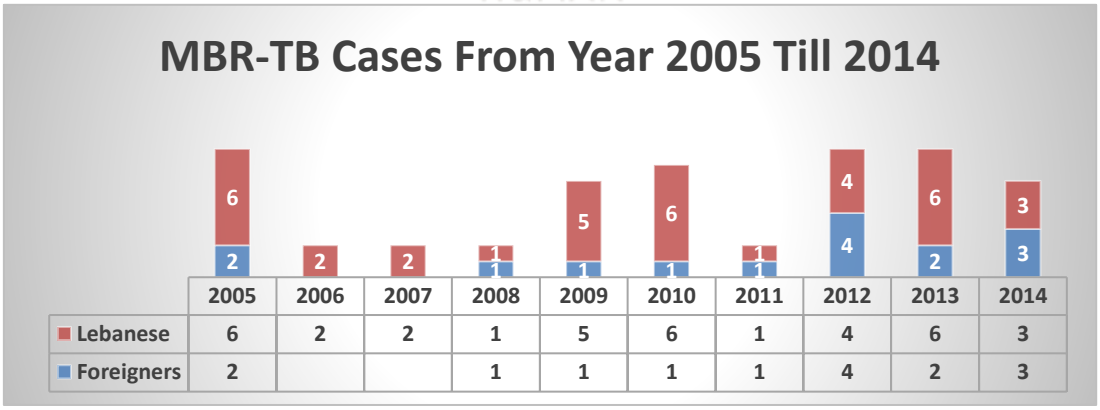

Figure 2: MDR-TB Cases in Lebanon 2005-2014

Mean age was 40 (16-70) distributed among males 45 and females 32, mean age in Beirut 37.5 (23-61), outside Beirut 41 (16-70). In addition, we had only one pediatric patient: 16-year-old Syrian female. About 2/3 (62.8%) of patients were males, with M: F in Beirut 2.3/1 and outside Beirut 1.6/1. Mean weight was 62 kg (36-97) distributed among males 64 kg and

females 58 kg (figure 3). Mount Lebanon alone, accounts for 41% of cases, another 18% live in Beirut. (Refer Figure 4). All patients coming from South Lebanon were living in Tyre.

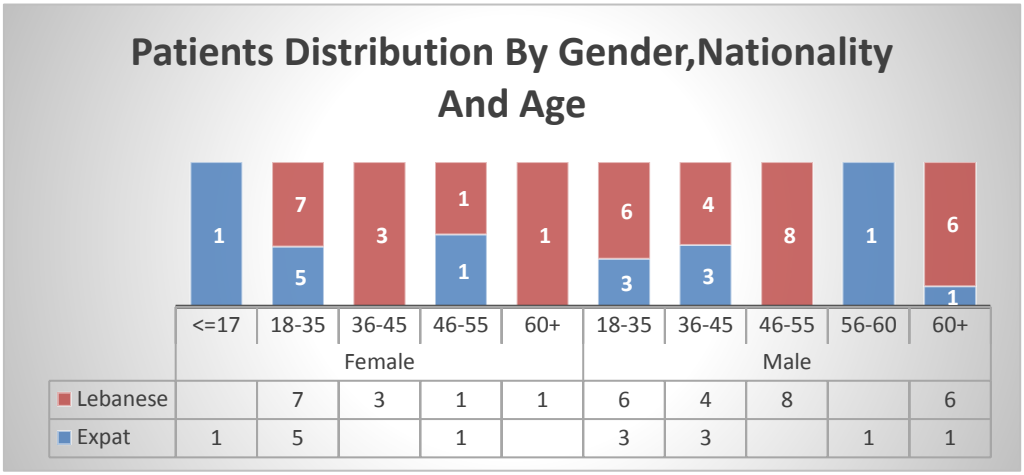

Figure 3: Distribution of Patients Based on Gender, Nationality, and Age.

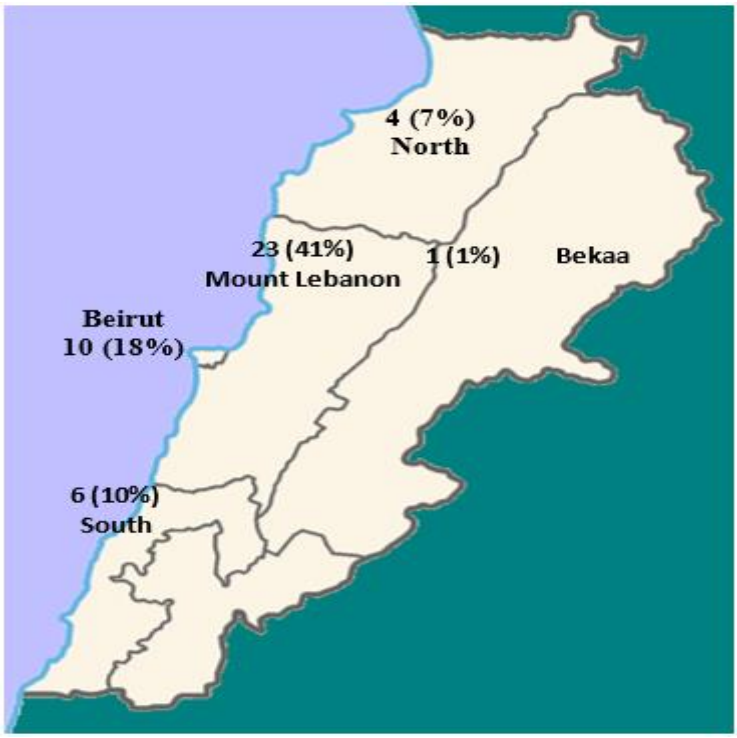

Figure 4: Geographic Distribution of MDR-TB in Lebanon 2005-2014

Documented risk factors included 8 DM II, 1chronic bronchitis, one chronic kidney disease, one patient was HIV+ with CD4 75 and Viral load 1.4 million at diagnosis, one patient had recurrent knee trauma and operations with subsequent osseous MDR-TB, and 76% were completely healthy.

MDR-TB Classification and resistance pattern:

Concerning the disease itself, we had 48 pulmonary cases versus three extra pulmonary (Divided into two Lymphadenitis and one osseous). 32 patients had secondary MDR-TB, 17(one third) had primary MDR-TB and two patients had MDR-TB with the failure of the treatment and readmission for retreatment. Percentages of primary and secondary MDR-TB came very similarly in both Lebanese and non-Lebanese patients. Primary resistance was highly dominant in both Lebanese and non-Lebanese patients in 2013 and 2014 and absent between 2005 and 2008. Patients were divided also based on the number and type of drugs to which the isolates were resistant: 26 (51%) had resistance to 4 drugs or more (44.4% in Lebanese vs. 66.7% in foreigners), 17 had resistance to three drugs and eight had resistance to only two drugs. No XDR-TB patients. The highest percentages of resistance were to Isoniazid and Rifampin, 100% and 94% respectively, and we had about 70% resistance for both Streptomycin and Ethambutol. Only one isolate was resistant to FQ.

Treatment:

Treatment was standardized including first-line drugs plus kanamycin, Ethionamide, Cycloserine and Levofloxacin with the introduction of Capreomycin since 2014. Of these patients, 41/51 (80.4%) had conversion, 36/41 (87.8%) had 2 consecutive negative smears or cultures in the first 6 months of treatment, with early conversions at first month: 8/41 (19.5%) and at second month: 25/41 (61%) and very minimal difference between Lebanese and non-Lebanese population. Common side effects of the treatment were GI symptoms (abdominal pain, nausea, vomiting, and diarrhea), myalgia, arthralgia and peripheral neuropathy, 3 patients had a severe headache, 3 patients had some hearing loss (1 died, 1 was lost to follow up (F/U), 1 cured), 1 patient had liver failure (died), 1 person had severe allergy to Rifampicin and another 1 had personality changes with new psychotic features (lost to follow up). Of the 51 treated patients, 26 (51%) had complete cure (55.6% Lebanese versus 40% foreigners), 5 completed the treatment without cure, 10 still on treatment for the time, 7 was lost to F/U (1/7 had left the country), 3 patients died (5.9%). Then Success rate (cure + complete) was 60% (70% in Lebanese versus 40% in foreigners) and 10 patients had the failure of treatment which represent 20% of the treated patients (11% in Lebanese vs. 40% in foreigners) (table 6).

Table 6: outcome of treatment in Lebanese and non-Lebanese patients

Values	Final Out Come rouping	Nationality Group		
		Foreign	**Lebanese**	**Total**
Number of Patients	Failure	6 (40%)	4 (11.11%)	10 (19.61%)
	Still On Treatment	3 (20%)	7(19.44%)	10(19.61%)
	Success Rate	6 (40%)	25(69.44%)	31(60.78%)
Total Number Of Patients		**15**	**36**	**51**

Death causes severity of disease (after 9 months of treatment), myocardial infarction (within the first month of treatment), and liver failure (after 6 months of treatment). The success rate was 100% in 2006, 2007 and 2009. Lebanese patients had the highest cure rate in the first 5 years of the study (Figure 7).

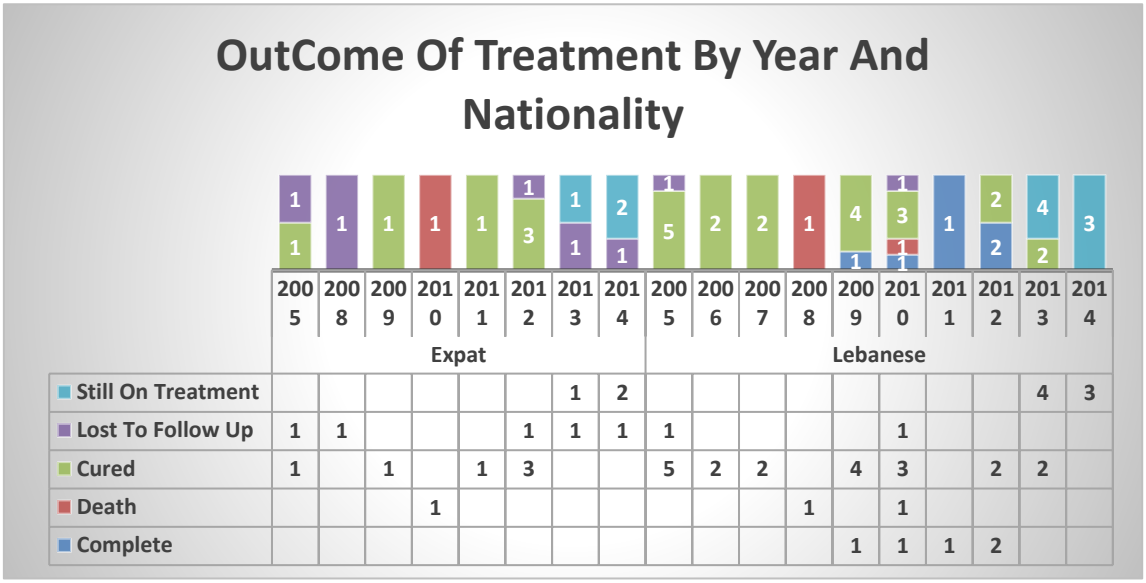

Figure 7: Outcome of Treatment in Different years: Lebanese Versus non-Lebanese

The Cure rate based on the number of drugs to which the isolate is resistant showed: 62.5% with 2 drugs, 76.5% with 3 drugs and 30.7% in 4 drugs and more. All 3-death cases happened when a patient had resistance to 4 drugs (Figure 8).

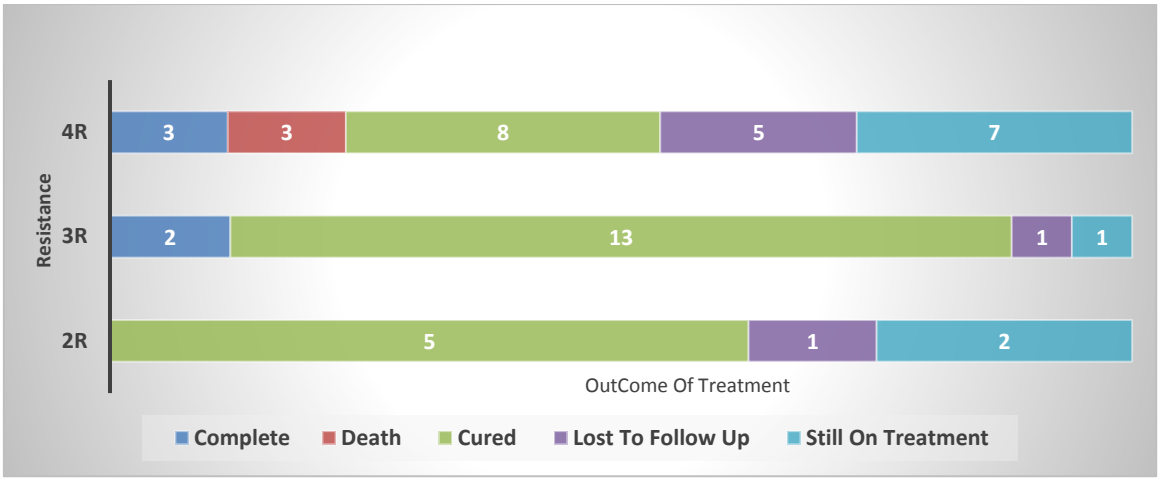

Figure 8: Outcome of Treatment Based on Resistance Pattern

When evaluating the outcome of treatment with patient's comorbidities prior to the disease, we found that 22/26 cured patients were previously healthy, the other 4/26 had diabetes II, 7 patients were lost to follow up: 4 healthy, 1 had HIV, 1 had chronic kidney disease and 1 patient DM II, 3 died: 1 had chronic bronchitis and another 1 had DM II.

And when comparing the outcome of treatment with the month of conversion after receiving the second line drugs, we noticed that all patients who died had no conversion, 2/10 of patients, who still on treatment for the time, had no conversion and the other 8/10, converted their smears/cultures within the first 6 months, 2/7 of patients had no conversion at time they were lost to follow up.

DISCUSSION

TB incidence in Lebanon has declined between 1999 and 2005 but started to increase in the last decade with the highest numbers in the last 3 years. MDR-TB in Lebanon, 56 patients was diagnosed between 2005 and 2014. The number of MDR-TB patients varies yearly but the last 3 years between 2012 and 2014 accounts alone for 41% of cases. About 30% of MDR-TB patients are foreigners, 60% of this non-Lebanese population were diagnosed in the last 3 years only. In a mean average less than 1% of TB cases are MDR-TB. These findings could be explained by the recent demographic changes in Lebanon and the surrounding, especially after the arrival of more than million refugees from civil Syrian war. It could be also due to the higher consciousness and the awareness programs since the arrival of the refugees. Another possible explanation is the improvement of diagnostic methods recently for example with the usage of GeneXpert in Lebanon since 2014. Finally the increasing needs for

foreigners employees (Examples: housekeeper, babysitter...) has led to increasing immigration from HBC (Ethiopia, Philippines, India, Pakistan...). In Lebanon most of MDR-TB Foreigners came from 2 HBC: Ethiopia and Russia and 2 surrounding countries in low socioeconomic conditions and war: Syria and Palestine. Patients are young, the mean age was about 40 (16-70), very similar to the latest national studies and data in other developing countries, reflecting primary transmission. We have only one pediatric case. M: F is two (7 in 2005), compatible male dominance with the literature and may be due to more frequent TB exposure in men. Mean weight was 59.2 kg (Low BMI is a risk factor in all types of TB infection). Concerning the geographic distribution, more than 40% of cases came from Mount Lebanon, with 18% in Beirut came second, compared with 33% in Mount Lebanon and 23% in Beirut in the latest national study. To Note all patients from the south live in Tyre possibly due to the contact of Tyre population with TB patients treated at Tyre sanatorium. Risk factors included DM II, chronic bronchitis, CKD and HIV. Most of patients were healthy, looking to the young population infected with the disease. We have only 1 MDR-TB HIV (+) patient in Lebanon in the last decade. We have 3 extrapulmonary cases: of which 2 lymphadenitis (which is the most common site of extrapulmonary TB) and 1 osseous (which occurred in the patient with recurrent knee infections and operations). About half of patients had resistance to 4 drugs or more (44.4% in Lebanese vs. 66.7% in foreigners), only 1 isolate was resistant to FQ. No XDR-TB in Lebanon since no DST for second line therapy until now. The highest resistance observed was to Isoniazid and Rifampin, whereas in 2005 the most common resistance isolates were for Isoniazid and Streptomycin. About 2/3 of cases are secondary MDR-TB and 1/3 are primary MDR-TB. These numbers are very similar in Lebanese and non-Lebanese population. Primary resistance was very high in the last 2 years (78.5% versus 33% in the 10 years). Secondary infection is caused by inappropriate treatment of sensitive TB cases and then a need for more organized DOT. Increasing primary infections is likely due to recent foreigner's immigration. Success rate in sensitive TB patients was alarming in 2014 and has declined, as low as 70% (93% Lebanese versus <50% Foreigners (because of lost to follow up)) to be compared with > 80% in the previous years and 86% worldwide. In MDR-TB, about half of patients, 51%, had complete cure (55.6% Lebanese vs. 40% foreigners), Success rate was 60% (70% Lebanese vs. 40% foreigners), to be compared with the average worldwide success rate of 48% in 2011. These success rate numbers are underestimated and can be as high as 75% (86% Lebanese Vs. 50% foreigners), if we exclude in the outcomes those 10 patients who still on treatment for the time and may become cured specially that 80% of them had converted their smears/cultures within the first 6 months of

treatment. The lowest cure rate happened with 4 drugs and more about 30% compared with 62.5% and 76.5% in isolates resistant to 2 and 3 drugs respectively, 5.9% of patients Died. Etiologies included: 1) Severity of disease (after 9 months of treatment) 2) Myocardial infarction (within the first month) and 3) Liver failure (after 6 months of treatment). All 3 death cases had no conversion and had resistance to at least 4 drugs. Failure of treatment was 20% (11% in Lebanese versus 40% in foreigners), 7 patients were lost to follow up after the intensive phase in sanatorium, which is very alarming and dangerous and lead to many questions concerning DOT's success in Lebanon. We may suspect better outcomes for the years 2013 and 2014 especially with the arrival of new 2nd line therapy drugs such as Capreomycin. Outcome of treatment is likely better with early conversion and less resistance. There were no big changes in the outcome of treatment with the different years. Common side effects of 2nd line drugs therapy included GI problems, arthralgia, Myalgia and peripheral neuropathy. Other severe symptoms: unbearable headache, hearing loss, liver failure, severe allergy and psychosis. In Lebanon, only patients who are suspected to have MDR-TB should be tested for sensitivity including: previously treated patients, all HIV (+) patients, contact with MDR-TB patients, TB not responding to first-line TB drugs within 2 months, disseminated TB as milliary and meningitis, patients coming from HBC, and patients (case by case) who were previously treated and lost to follow up. Also patients are not allowed to take flights before 15 days and 2 months of treatment for sensitive and resistant TB patients respectively. We were obliged to exclude 5 patients from the study because they had no documented data or files. This exclusion may interfere with the results, but 4 out of these 5 patients had left the country and are unreachable so we couldn't include them in our study. Weakness of the study include: Size of studied population, results are an underestimation of the reality of MDR-TB in Lebanon because of difficulties in screening and diagnosis, lack of 2nd line DST in a way XDR-TB diagnosis and individualized treatment regimen still impossible, patients who were lost to follow up and didn't complete their treatment. The results of this study represent the entire Lebanese population between 2005 and 2014 because the data of every patient diagnosed with MDR-TB in Lebanon was carefully collected; it gives us an idea of the epidemiology of MDR-TB in our country and is a sign of increasing need for awareness and public health reactions. The big debate of today concerning TB in Lebanon and worldwide is concerned about screening issues: which population should be screened for both sensitive and resistant TB? And about latent TB infection treatment: Treating those patients is it preventing active TB or increasing risks for MDR-TB.

CONCLUSION

MDR-TB is a new entity in Lebanon requiring awareness and attention. Lebanon is a country where the population is affected by thousands of immigration and emigrations yearly and is situated in the Middle East region under remarkable changes recently. Our study represents MDR-TB in all Lebanon in the last decade since the beginning of MDR-TB treatment; it included only 51 patients but could be a new beginning in the understanding of this disease and to turn on an alarming system. Improving both primary and secondary prevention in either sensitive or resistant TB patients, amelioration of patient's compliance to treatment, Sanatorium abilities and DOTs strategies, regular surveillance programs, serious intervention of the WHO and public health to control the disease and increasing awareness on this subject will be essential in the upcoming years to confine the problem and lead us to the hopes of disease's elimination.

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