Multidrug resistant TB and extensively drug resistant TB

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INTRODUCTION

Resistance to anti-TB drugs is not an emerging phenomenon, but a process closely related to the implementation of chemotherapy against TB. Clinical evidence to prove the development of resistance to anti-TB drugs was provided by the *Medical Research Council* team in 1948, shortly after using streptomycin in (as?) monotherapy for TB treatments [1]. As isoniazid, PAS and streptomycin were first used for therapy, the idea of primary and secondary resistance became evident, setting the basis, along with microbiological research carried out by emerging figures such as *Mitchison, Canetti and Grosset* [2], for current two-phase anti-TB chemotherapy. The latter combines the use of rifamycin and isoniazid, which attain high success rates against TB when implemented with correct therapy compliance, but imply high risks of therapy failure if used with inappropriate regimens, or when prescription errors, lack of resources or poor adherence to treatment occur. In addition to this, isolating resistant strains which may be transmitted to the community producing primary resistance substantially reduces first line regimen healing rates[3]. Poverty, overpopulation and the lack of resources and adequate TB treatment programs, along with the appearance of HIV, have caused the development and spread of multi-resistant TB strains with almost no therapy options.

MULTIRRESISTANT TB APPEARANCE AND SPREAD

In consequence to the success of anti TB treatment, both TB morbidity and mortality rates decreased during the 60's and 70's of the twentieth century. Therapy failure rarely occurred and multiresistant TB was considered, as far as its incidence is concerned, a minor problem usually associated to incorrect adherence, while primary multi-resistance was very rare. Unfortunately, the emergence of HIV during the 80's triggered a dramatic rise in TB incidence, more strongly in underdeveloped countries, first in Sub-Saharan Africa, followed by South East Asia several years later. Within this context, the World Health Organisation (WHO) proclaimed TB as a world healthcare crisis in 1993[4]. In 1994, along with the International Union Against TB (IUATLD), the World Healthcare Organisation started the "*Global Project on Antituberculosis Drug Resistance Surveillance*", just at the time, during the first half of the 90's, when the first multiresistant TB outbreaks where taking place in Europe and the U.S., mostly affecting patients infected with HIV. These patients displayed "explosive" transmission patterns, along with high attack rates and short incubation periods caused by their immunodeficiency status and the lack of correct means to avoid TB airborne transmission in hospital units, accommodations and penal institutions affected by TB outbreaks[5-7]. In Spain, a *Mycobacterium bovis* strain resistant to all first line drugs, quinolones, injected agents and to almost all available second line drugs, caused a major epidemic outbreak affecting 49 patients in a hospital's HIV Unit in Madrid, from 1991 to 1995[8,9]. The outbreak spread, finally affecting at least 114 patients from 22 Spanish hospitals and two further contacts who later developed the disease in Netherlands and Canada.

The first global data concerning resistance to anti TB drugs, obtained by the WHO and IUATLD, were published in their 1997 report, and matched the results of the resistance surveillance carried out in monitoring labs from 35 different countries around the globe since 1994 till 1997[10]. Evidence of primary multi-resistance was found in all 35 countries subject to study. The primary resistance rate median was 1.4 %, although it reached up till 14.4 % in Latvia and rose over 2% in one out of three countries. It did not come as a surprise that those countries with insuf-

ficient anti TB programs were the most affected by multi-resistance. Global resistance figures provided by the report clearly depicted the full extent of this healthcare issue in some areas. In Latvia, 30% of patients under anti TB treatment were infected by multi-resistant strains, in Russia this figure reached 5%, 10% in Dominican Republic and 13% in Delhi (India).

Subsequent surveillance reports dating from 200, 2004, 2008 and 2010 increased the number of countries subject to study to 109, finding evidence that, whereas in countries with low TB incidence resistance rates remained stable, they become dramatically high in some regions, such as the Baltic republics, Russians, some of the former Soviet Union republics (Moldavia, Azerbaijan, Kazakhstan, Uzbekistan), South Korea, Peru and some Chinese and Indian provinces[11, 12].

In the 36th Edition of the "*World Conference on Lung Health*" from October 2005, data regarding a world surveillance program on second line drug resistance, carried out by the WHO's Reference Laboratories together with US Centres for Disease Control and Prevention (CDC), was presented. This was the first time the term "extensively drug resistant tuberculosis" (XDR-TB) was used. In the Conference on Retroviruses and Opportunistic Infections (CROI) from February 2006 an outbreak of XDR-TB in the region of Kwa-Zulu Natal in South Africa was reported. Epidemiologic concern on the emergency of MDR-TB and the definition of XDR-TB was jointly published by the CDC in the journal *Morbidity and Mortality Weekly Report* (MMWR), as well as by the WHO in the *Weekly Epidemiologic Record* from March 2006[13, 14]. The original definition included those TB cases with a strain resistant to isoniazid and rifamycin, as to at least three of the six second line agents: aminoglycosides, polypeptides (capreomycin), fluoroquinolones, thioamides, cycloserine and PAS. 17,690 isolates dating from 2000 to 2004 were studied, among which 11939 came from South Korea (11% of which were MDR). 5,751 isolates came from other countries, 2,222 of which (39%) were also MDR. Out of the 3520 MDR isolates, 347 (10%) were XDR (15% of the Korean MDR strains and 7% of the MDR strains of other countries). XDR strains were more frequently found in South Korea and in other countries from Eastern Europe and Western Asia. Excluding Korean strains, the total number and proportion of XDR strains had suffered a significant increase during the study period (14 strains- 5%, in 2000; 34 strains- 7%, in 2004). The report included information on the evolution and therapy response of 490 MDR-TB cases, and 115 XDR-TB cases treated in Latvia from 2000 to 2002. Failure and death rates reached 17% in MDR cases and 26% in XDR cases (relative risk 1.5; CI95%:1.1-2.2).

In October 2006 the first meeting of the "*Global XDR Task Force*" was held in Geneva, under the management of the WHO. The definition of XDR-TB was then reviewed and it was suggested that it included those strains resistant to rifampin, isoniazid, and fluoroquinolones and to at least one of the three injected second line agents (amikacin, kanamicin or capreomycin). There were two reasons for changing the definition. In the first place, technical and reproducibility difficulties related to susceptibility studies regarding some second line agents caused the first definition to become inaccurate. Secondly, the determining factors for therapy failure were proven to be both resistance to quinolones and injected agents, as well as the institution of regimens without these drugs for the treatment of MDR-TB.

The latest official data regarding multi-resistance correspond to the 4th report of the WHO. It estimated between 390,000 and 510,000 new cases of MDR-TB worldwide for 2008. This figure corresponds to 3.6 % of all the cases (CI95%:3.0-4.4). 50% of the patients were diagnosed in China and India. In 2008, around 150,000 people passed away due to MDR-TB. The report includes representative data on second line resistance from 46 countries. In those countries, 5.4 % of MDR-TB cases were XDR. When the report was drafted, 58 countries had reported XDR-TB cases[11-12].

Data regarding MDR-TB surveillance during 2008, in all 25 countries of the European Union and the European Economic Area[15] were recently published, with 28,295 isolates given account of, which represent only 34.4% of the 82,611 TB cases reported that year. MDR-TB strains represented 6% of all isolates, 7.3% of MDR-TB cases were XDR-TB, and 13 out of the 25 countries reported some XDR-TB cases. Estonia, Latvia, Lithuania and Romania presented the highest MDR and XDR strain rates. Spain reported 8,214 TB cases in 2008, 4,493 with positive culture, 1,628 of which underwent sensitivity testing; 76 MDR-TB cases (4.7% of all strains subject to study), 3 being XDR. 31 isolates came from 1080 patients without any previous treatment, depicting a primary multi-resistance rate of 2.9%. The situation in some Eastern European countries is alarming with primary multi-resistance rates reaching 4.3% in Romania, 9% in Lithuania, 12.1% in Latvia and 15.4% in Estonia.

It becomes clear that MDR-TB and XDR-TB is among us, and demands a coordinated effort coming from physicians, microbiologists and epidemiologists, in order to avoid its spread.

The recent encounter with the XDR-TB epidemic in KwaZulu-Natal, South Africa, depicts how dangerous these strains can become when they spread among an extremely susceptible population, due both to HIV co-infection and the lack of basic infection isolation and control measures. The first data corresponding to the TB cases reported in *Tugela Ferry* district between January 2005 and March 2006 depict that out of the 53 XDR-TB patients diagnoses, 52 died within a median of 16 days after diagnosis[16]. 26 out of 47 patients (55%) had never been diagnosed or treated against TB before, and 28 out of 42 (67%) reported a recent stay in hospital, pointing out the importance of control measures to avoid nosocomial transmission. All HIV serological tests performed with 44 patients turned out positive. The majority of first XDR-TB patients were not given second line drugs, for multi-resistance was not taken into account as a possible treatment outcome. During 2006 and 2007, 5,612 MDR-TB cases were reported in *KwaZulu-Natal* province, 515 of which were XDR. The current situation in South Africa is alarming. With a 48 million population, HIV prevalence reached 11% in 2008, and the reported TB rates rise to 900 cases per 100,000 people. The South African National Health System laboratories reported 388,802 new TB cases in 2008, out of which 576 were XDR and 6,219 were MDR. For 2008, the WHO estimated 10,000 MDR-TB cases (CI95%:7,500-13,000) taking into account new TB infections and relapse in South Africa.

DIAGNOSTIC MICROBIOLOGY OF MULTI-RESISTANT TUBERCULOSIS

The traditional diagnostic microbiology of resistant TB consists of sensitivity testing in solid culture medium, using *Canetti's* "proportion method"[17]. Considering that there is always a certain proportion of "resistant" bacteria in a sensitive population, resistance is defined as the growth of at least 1% of the bacterial inoculation growing along with a "critical" antimicrobial concentration. This method is arduous, and demands obtaining a certain amount of inoculation from primary isolation and incubating plates long enough to reach perceptible growth (at least 28 days for the traditional method).

Although the sensitivity test in solid medium is still the reference technique, non-radiometric liquid mediums, such as MGIT960 (Bactec *Mycobacterial Growth Indicator Tube, Becton Dickinson Diagnostic*), are the most commonly used systems in laboratories, both for mycobacterium primary isolation and sensitivity tests[18, 19]. Liquid mediums enable accelerating the process and obtaining results faster, usually with an excellent match to results from traditional solid culture methods. Nevertheless, they entail a major inconvenience: results may be varied by culture contamination coming from environmental mycobacterium. Despite the use of liquid mediums, between isolation and running the sensitivity test it is still unattainable to confirm the resistance of any strain until 6 weeks after diagnosis, maybe causing unacceptable delays when taking therapy decisions. Due to this, during recent years molecular techniques to directly detect the most frequent genes involved in resistance to rifampin (rpoB and katG genes) have been put into practice. When resistance is highly suspected (in view of poor treatment response, or due to epidemiologic circumstances of the case), using molecular biology can provide the diagnosis regarding direct sampling with acid-fast staining or the first colonies which appear in culture[20]. Table 1 depicts the main genetic determinants of drug resistance in *M. tuberculosis*.

Sensitivity tests run with first line drugs (isoniazid, rifampin, ethambutol, pyrazinamide and streptomycin) entail few technical problems and little difficulty interpreting its results, with critical concentrations which split sensitive strains off resistant ones being accurately established. Furthermore, methods based on liquid mediums provide reproducible results. Studies carried out by the WHO and the IUATLD between 1994 and 2002 within the context of the global resistant TB surveillance project[12], depict that sensitivity and specificity of the tests run with rifampin and isoniazid were better than those of ethambutol and streptomycin (sensitivity: 99% for INH, 97% for RMP, 91% for SM and 89% for EMB; specificity: 98% for INH, 97% for RMP and 94% for both SM and EMB). On the contrary, sensitivity tests run with second line drugs involve serious reproducibility problems, due to the lack of a methodology standardisation (incubation time, temperature, pH and medium), to the instability of some of the drugs and to the little margin existing between concentrations that inhibit sensitive and resistant population growth. The results match better for quinolones, amikacin, kanamicin and capreomycin, whereas

Table 1. AntiTB agents and genes most frequently involved in resistance

Drug	Involved genes	Mutation frequency
Rifampin	Subunit B RNA (rpo)	96%
Isoniazid	Enoyl-ACP reductase (inhA) Catalase-peroxidase (katG) Alquil-hydroxyperoxiredoxin (ahpC)	10-20% 30-60% 2-8%
Ethambutol	Arabinosyltransferase (embC,A,B)	80%
Streptomycin	Ribosomal protein S12 (rpsL) 16S portion of ribosomal RNA (rrs)	52-59% 8-21%
Pyrazinamide	Pyrazinamidase/nicotinamidase (pcnA)	72-97%
Quinolones	SubunitA of DNA gyrase (gyrA)	75-94%

they match worse for thioamides, cycloserine and PAS.

MULTI-RESISTANT TUBERCULOSIS' PROSPECT AND TREATMENT

Before anti-TB chemotherapy, approximately 3 out of every 4 patients suffering from active lung disease passed away during the first five years after the start of progressive illness symptoms. 25% survived, experiencing chronic TB manifestations or even spontaneous recovery from the disease. The use of standard protocols including the use of rifampin and isoniazid succeeds in healing TB caused by strains sensitive to first line drugs in almost 95% of the cases. The prospects for MDR-TB differ, depending on therapy protocols used and incidence of comorbidity, being immunodeficiency, and therefore HIV infection, factors causing very negative prospects. *Johnston et al* [21] have recently published a meta-analysis depicting the results of 31 studies carried out in 21 different countries between 1973 and 2006, with the vast majority of series being studies in retrospect. In 26 studies which only included response at the end of the treatment (4,959 patients), 62% experienced positive response, 11% passed away, 8% failed and 13% lost surveillance. In 9 trials (carried out with 1,583 patients) including later monitoring, 2% experiencing recidivism after having completed treatment. Male condition, alcohol abuse, low body mass index, resistance to fluoroquinolones and the appearance of XDR pattern are determining factors in therapy failure, whereas the use of quinolones, therapeutic surgery and the lack of previous treatment are usually related to better prospects.

Multi-resistant TB chemotherapy must include a minimum of 4 potentially active drugs, sequentially chosen (Table 2). When possible, all active first line drugs must be included (group 1), one injected agent and one quinolone, except for cases where reliable microbiological evidence proves the resistance of the isolate. As far as treatment duration is concerned, the initial phase, which must include some injected agent, lasts for a minimum of 6 months (or at least 4 months after culture negativisation) and is then followed by a continuation phase (without injected drugs) which will last a minimum of 18 months after culture negativisation [22].

Therapeutic surgery in multi-resistant TB cases is taken into consideration when patients suffer localised lung damage and still have enough respiratory capacity to endure lung resection. Data published by some leading institutions with ample experience in surgery [23] depict excellent therapy results when surgery is combined with medical treatment including quinolones and injected agents. Patients whose resistance profile indicates a probably adverse prospect and those who, despite monitored treatment, fail due to persistent positive cultures after 4-6 months should be taken into consideration as subject to therapeutic lung surgery carried out by a specialised surgery team.

MULTI-RESISTANT TUBERCULOSIS' CONTROL AND TRANSMISSION

It has been postulated that multi-resistant strains may suffer from ecological disadvantage as far as their dissemination is concerned, in opposition to their self replication capacity and virulence ("*fit-*

Table 2. Classification and use of antiTb agents for MDR-TB

Group 1	**First line**: Isoniazid, Rifampin, Ethambutol and Pyrazinamide	Upon definition both MDR and XDR-TB isolates are resistant to rifampin-isoniazid. Ethambutol and Pyrazinamide must be used if in vitro activity can be found. Some authors recommend using high doses of isoniazid with low resistant strains, which could also be used to counteract against ethionamide resistance.
Group 2	**Fluoroquinolones**	A quinolone must always be used as far as possible. Ofloxacin, levofloxacin, moxifloxacin and gatifloxacin are the most commonly used agents. If levofloxacin is used high doses are needed (15mg/kg: 750-1000mg/day)
Group 3	**Injected agents:** Stremptomycin, Capreomycin, Kanamicin and Amikacin	MDR- TB therapy regimens must always include and injected agent which will be chosen on account of the therapy history and sensitivity tests. The logical sequence of election is : Streptomycin-Capreomycin- Kanamicin- Amikacin
Group 4	**Second Line "less active"**: Thioamide, cycloserine, PAS	It includes in order of preference: thioamides (prothionamide and ethionamide), cycloserine and PAS. Induction regimen must be completed with at least 4 active agents.
Group 5	**Alternatives of doubtful activity or effectiveness:** Clofazimine, Amoxicillin-clavulanate. Linezolid, Carbapenem, thiazetacone, claritromycine	These are agents with a doubtful effectiveness which are used when no other therapy option is available (less than 4 active agents). In order of preference it includes: clofazimine, amoxicillin-clavulanate, linezolid, carbapenems, thiazetacone, claritromycine.

ness") caused by mutations generating resistance to anti-TB agents[24]. This theory is partly based on experiments carried out with animals infected by *M. Tuberculosis* strains carrying mutations in their catalase-peroxidase katG genes, which entail less virulence than wild strains. Nevertheless, there are strong arguments against this thesis. Firstly, it has been proven that some katG mutations that cause high-level resistance to isoniazid do not inhibit catalase enzymatic activity in bacteria. Secondly, the active spread of the Beijing strain, usually connected to multi-resistance, leads to the idea that although some resistance mutations might undermine bacterial "fitness" to some extent, as far as epidemiological effects are concerned, we cannot assume that multi-resistant strains are less infective or virulent than sensitive ones [25].

An important aspect of multi-resistant TB is the risk of nosocomial dissemination, in enclosed institutions such as accommodation facilities, internment centres and detention facilities. The first TB control guidelines for penal institutions were published by the WHO and the International Committee of the Red Cross (ICRC) in 1998. In most epidemiologic studies published, TB incidence in prisons and internment centres was10 to 100 times higher than among the general population. This way, in many countries TB incidence rates in prisons rise over 3000 cases per 100,000 people - year. This is partly due to intern's higher vulnerability (caused by acute HIV infection rates, drug addiction, alcohol dependence, malnutrition, and poor socio-economic conditions), but also due to the physical and population density conditions in prisons, which logically encourage aerial dissemination of *M. tuberculosis*. Incidence of MDR-TB is also higher in penal institutions. Multi-resistance rates reaching over 10% have been reported in some Russian prisons, as well as in some former Soviet Union republics (Georgia, Azerbaijan) and Zambia, out of which 7% are XDR strains. Penal institutions contribute to TB dissemination, regarding interns, staff and visitors [26-28].

In theory, prisons should be the perfect context for early TB diagnosis and therapy monitoring. This is far from reality in several countries, where late diagnosis is quite usual and screening, therapy surveillance and healthcare control programs either do not exist or cannot be implemented until accurate responsibilities and sufficient resources are set and provided.

The basis for TB control in prisons relies on tuberculin screening and early diagnosis, monitored treatment, respiratory protection and isolation measures, and coordination with the pertinent

healthcare system in order to ensure external patient surveillance. The use of respiratory protection masks (at least N95 or FFP-II) is essential in order to avoid TB transmission to healthcare staff; properly trained to use them (any filter is useless if face adjustment is inadequate). Prevention measures are extremely important after procedures which may provoke cough or aerosols (the use of nebulisers, bronchoscope, induced sputum procedures…) [29].

NEW DRUGS FOR TREATING MULTI-RESISTANT TUBERCULOSIS

Due to its little commercial interest, the creation and development of new drugs for treating multi-resistant TB has been quite limited. The "TB Alliance" initiative, set up in 2000, is a non-profit organisation working as a network of public and private organisations whose joint efforts are focused, along with other aims, on the development of new drugs for treating TB [30].

Currently, there are several drugs active against *M. Tuberculosis*, in different development stages. Some belong to well known groups, such as the new fluoroquinolones: moxifloxacin and gatifloxacin, which attain more in vitro activity than ofloxacin [31] but entail cross-resistance. Due to this, they are not an option against strains already resistant to other quinolones. Oxazolidinone PNU 100480 also attains excellent activity against mycobacterium, in vitro, and behaves better than linezolid in murine models [32].

Among the new drugs from antimicrobial groups in foremost development stages, we must highlight nitroimidazoles OPC67683 and PA824, diarylquinoline TMC207, pyrrole LL3858 (Sudoterb), and diamine SQ109 [22, 33-36].

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