INTERNAL MEDICINE JOURNAL

Internal Medicine Journal **41** (2011)

EDITORIAL

The 'frozen state' of drug-resistant tuberculosis: notes from the field in Abkhazia

The success since 2004 in stabilising the global tuberculosis (TB) epidemic is being undermined by the emergence of drug-resistant TB (DR-TB). This form of TB is more difficult and costly to diagnose, treat and cure. In 2009, the World Health Assembly declared DR-TB a 'global public health threat' that threatens to undermine the sustainability of TB programmes.[1] This global resolution aims to achieve universal access to diagnosis and treatment of DR-TB by 2015.[2] However, only 11% of notified multi–DR-TB (MDR-TB) cases received treatment in 2009.[3] The response to DR-TB must focus on the strengthening of national TB programmes and on the scaling up of services to diagnose patients and make treatment accessible. We need to pursue the goal of universal access to these services, coupled with the urgent development of new drugs, point of care diagnostics and tools to achieve the ultimate aim of eradication of the disease.

DR-TB includes MDR-TB, defined as resistance to at least isoniazid and rifampicin – the two most efficacious drugs for treating TB – and extensively DR-TB (XDR-TB), which has additional resistance to a fluoroquinolone (levofloxacin, ofloxacin, moxifloxacin) and one or more second-line injectable antibiotics (kanamycin, amikacin or capreomycin) – the most effective of the second-line drugs. It also includes monoDR-TB or polyDR-TB – resistance to any other first-line drugs that is not MDR-TB or XDR-TB. These patterns of resistance are important to report, as the standard 6-month TB treatment regimen cannot be used if present. Often second-line drugs are required, though rarely available in most settings, resulting in treatment failure and amplification of resistance.

TB in the former Soviet Union

The former Soviet Union comprises the Russian Federation, parts of Eastern Europe, central Asia and the Caucasus and contains 12 of the 27 global high-burden MDR-TB countries. The TB epidemic in this region is different to Africa and other areas in Asia in its context (middle income, low HIV prevalence) and aetiology (collapse of health systems, unregulated drugs and transmission in prisons). During the Soviet era, Russia possessed a well-developed health system with innovation and development. The Soviet republics were part of a large central organisational structure with Moscow at the centre. Health structures were vertical, with hospitals for each specialty. The collapse of the Soviet Union in 1991 brought a transition to a market economy and open society. However, socio-economic conditions worsened, and there was collapse and decentralisation of the health system.[4] Funding for health was not a priority, in particular TB. The republics and regions (or Oblasts) were devoid of functioning national health/TB programmes. The pharmaceutical industry was deregulated, leading to poor-quality drugs, freely available private TB drugs and frequent stock-outs in government facilities. The real nidus for TB was the overcrowded prisons with separate and weaker healthcare systems. Finally, there was an initial absence of international health factors, particularly with the relics of political isolation from the West. In Russia, TB mortality almost doubled in 20 years to 1999 and was the highest in Europe at 20 per 100 000.[4] Drug resistance reached rates close to the highest in the world.

Abkhazia, a territory in the Caucasus, nestled between the Black Sea, Russia and Georgia, was once the seaside jewel in the crown of the Soviet empire. Since a horrific ethnic conflict in 1992, it has become a 'frozen state' – largely unrecognised by the international community because of its self-declared autonomy from Georgia.[5] Abkhazia is isolated geopolitically and under economic sanction. Their health system functions poorly, and a new threat has emerged – DR-TB. Médecins Sans Frontières (MSF) has supported the local health authorities in Abkhazia, Georgia and the region in treating patients with DR-TB since 2000.

> I first met Aslan[a] when he presented to the TB hospital in Sukhum(i), Abkhazia with cough and fevers. This 30-year-old Abkhazian man had been imprisoned in overcrowded condition in Russia for 13 years where he acquired tuberculosis. He was treated with multiple regimens with partial resolution of symptoms, however when he was released and went back to live with his family, his symptoms returned. His sputum was sent on a 20-day journey to the reference laboratory in Belgium. Three months later, after the slow diagnostic culture process – the results of drug-susceptibility testing showed he had extensively drug-resistant tuberculosis (XDR-TB). Despite his understandable skepticism of doctors and TB treatment, he started taking multiple drugs as prescribed.

[a]Names of patients have been altered for publication.

Although he initially felt better, the side effects were intolerable, and he was soon vomiting every day. In addition, he was asked to remain in hospital while infectious and smear-positive. For Aslan the outlook was bleak: he had no livelihood. He knew he would die from his TB. He did not continue his treatment. The local doctors and MSF team screened his family and, unfortunately, his 16-year-old niece, a household contact, was infected with TB, most likely XDR.

In Abkhazia, MSF facilitated drug susceptibility testing during 2000–2010: 18% of all suspected cases (smear positive and negative) had MDR-TB, including 2% with XDR-TB. Community transmission or primary resistance of DR-TB is evidenced by the fact 37% of patients with MDR-TB never had TB before. Only one third of these patients had a known contact with another person with MDR-TB.

Cure of DR-TB is possible, necessary and cost-effective

Recent modelling studies have shown that if MDR-TB is not treated or addressed, it will out-compete the drug-susceptible strains and become the predominant type.[6] Treatment and care of patients with DR-TB are possible, achievable and necessary. The best DR-TB programmes have cure rates of 80% for MDR-TB and 60% for XDR-TB.[7] The successes of current programmes are moderate. Globally, an average of 62% of patients are cured or complete treatment, 13% default, and the remainder fail or die.[8]

Treatment of DR-TB requires financial investment – mostly drugs, but also for diagnostics, infection control, patient support and directly observed therapy (DOT) staff. First-line TB drugs cost US$19 per patient for the 6-month treatment course.[9] Second-line TB drugs are available for approved programmes through the Global Drug Facility. This reduces drug costs from around $20 000 per patient to $4400–$9000.[10] Treatment of MDR-TB, however, is a cost-effective public health intervention, even in low- and middle-income settings.[11,12]

The treatment of DR-TB is challenging for health providers and an arduous journey for the patient. Current treatment regimens are constructed with second-line drugs – old compounds that are less efficacious, more toxic and more costly.[2] The evidence base for guidelines is of low quality with no randomised controlled trials. In 2011, the World Health Organization (WHO) published an update to its DR-TB guidelines, which included a meta-analysis of the three published systematic reviews. Current principles of treatment include:[13,14]

- At least four likely effective drugs should be used when MDR-TB is suspected
- Regimens should include at least pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide (or prothionamide), and either cycloserine or p-aminosalicylic acid
- Treatment duration is at least 20 months. The intensive phase involves the use of an injectable agent for at least 8 months and 4 months after culture conversion.

The global drug development pipeline for TB remains insufficient to address the needs of treatment.[15] The last novel compound invented for first-line TB therapy was rifampicin in 1963, and in the past decade, only six compounds have been making the progression through clinical trials. The most exciting development has been the development of a pilot 9-month short-course regimen for MDR-TB in Bangladesh, with cure rates of almost 90%.[16] It is currently being explored further in a multicentre study, and preliminary reports from Africa are promising.

Treating individuals with DR-TB – beyond the drugs

Patient support is an integral part of DR-TB treatment and should be directly observed by a treatment supporter. The medical treatment should be supported by nutrition (food packages), health education, social (transport) and psychological support. Implementing these models of care in contexts where health systems are weak is challenging. A community-based model of care involves the DOT provider having a central role as a treatment supporter and avoiding prolonged hospitalisation. Such a model has been shown to be effective in resource-limited environments and is recommended by the WHO.[17,18]

In the programme in Abkhazia a multi-disciplinary approach has been adopted by MSF and the local TB hospital, with weekly team meetings between physicians, nurses, TB educators and social workers. After initial hospitalisation, patients were supported through treatment with flexible treatment delivery – community DOT providers, transport subsidy, food packages and home modification for infection control. There is an ongoing attempt to link TB care between the health and prison systems. However, these efforts are constrained by the geopolitical situation in this post-conflict setting. There is a limited programmatic or strategic approach to TB care and local capacity is low. Around 20% of patients default from treatment and poor adherence has resulted in amplification of resistance.[19] Patients are from vulnerable groups – 41% of DR-TB patients had a history of incarceration, 54% harmful levels of alcohol, 11% a history of intravenous drug use and 3% were homeless. In addition, there

were internally displaced persons from the conflict. Conversely, MSF has successfully scaled-up and handed over a DR-TB program in the town of Zugdidi, on Georgian side of the 'frozen border' to the national TB program.

DR-TB on the global stage

Each year an estimated 500 000 people acquire new infection with MDR-TB and 150 000 die.[3] The incidence is rapidly increasing each year.[20,21] Currently, there are an estimated 1.5 million people living with MDR-TB, including 50 000 with XDR-TB.[22] It is important to note that global data quality on drug resistance is poor. It is limited by inaccurate reporting/recording and inadequate laboratory capacity for drug-susceptibility testing. In particular, resistance is largely unquantified in Africa with only 12 of 46 countries having conducted a national DR survey since 2000.[9] Furthermore, WHO data underestimates the true burden of DR-TB, as it is based only on drug-susceptibility testing from smear-positive cases, neglecting smear-negative and extra-pulmonary TB.[23]

Barriers to scaling up comprehensive TB care

The programmatic management of DR-TB requires a comprehensive public health approach. It is built on having good basic TB control to prevent DR-TB emergence. This is an enormous challenge for resource-constrained countries, and the current assistance of the international community is far from adequate. The challenges are

- Funding gaps: US$7.1 billion is needed to treat MDR-TB for the period of 2011–2015.[2]
- Limited local political will.
- Lack of skilled human resources.
- Lack of laboratory capacity for diagnosis and reliance on specialised tests: the new geneXpert rapid test (real time PCR) can diagnose MDR-TB in less than 2 h but requires substantial financial and human capacity investments.[24]
- Inadequate production and high costs of second-line drugs.
- Urgent need for more effective and less toxic drugs, and shorter treatment regimens, but there is limited investment in new drug development or trials of shorter regimens.
- Need for the development of innovative context-adapted community-based care models.
- Ineffective infection control measures are a key driver of the DR-TB epidemic, including in healthcare facilities. Infection control measures need to be in place in all healthcare settings, together with initiatives to reduce community transmission, including point of care diagnostics and effective treatment.

Conclusions

Drug-resistant tuberculosis is an increasing problem that threatens the substantial gains in TB control that have been made globally in the last 20 years. Despite difficulties, DR-TB can be successfully treated with currently available diagnostics and treatments. The WHO Stop TB Plan for 2011–2015 calls for universal access to diagnosis and treatment for DR-TB by 2015. As can be seen from Abkhazia and many other countries, however, the gaps between guidelines and on the ground implementation remain large. The threat of DR-TB is imminent in the Australasian region – Simpson highlighted the alarming rates of DR-TB in Papua New Guinea in last month's editorial in the *Internal Medicine Journal*.[25] Without urgent action and political commitment from donor agencies, the Global Fund and governments, the ambitious goals set will not be reached.

Received 5 October 2011; accepted 10 October 2010.

doi:10.1111/j.1445-5994.2011.02617.x

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