Editorials

Multiple drug resistant tuberculosis

Tuberculosis, despite major advances in our understanding of communicable diseases, remains the most important infectious cause of mortality in the world today. Almost 8 million new cases occur each year with nearly 3 million deaths.[1] Over 95% of tuberculosis cases occur in the developing world, where tuberculosis accounts for over 25% of all preventable adult deaths.[1] The first effective antituberculous chemotherapeutic agents, streptomycin and p-amino salicylic acid (PAS) were discovered in the late 1940s, and early animal and then human trials quickly proved their efficacy. Drug resistance emerged quickly, however, when single agents were used. The principles of successful treatment using combinations of drugs were subsequently established in a series of landmark studies conducted by the British Medical Research Council and its partners. The use of PAS with streptomycin reduced the emergence of resistance from 70%, when streptomycin was used alone, to 9% when the drugs were combined. If appropriate drugs, therefore, were given in combination for an adequate period of time, then over 95% of patients would be cured. The discovery of new drugs enabled regimens to shorten to the current six to nine month standard protocols and work is progressing, albeit on a modest scale, to reduce this period further.

Although resistance to single drugs occurred soon after their first use, it is the emergence of multiple drug resistance (MDR)—that is, resistance to isoniazid and rifampicin with or without resistance to other drugs, that has aroused the most alarm. MDR tuberculosis in the USA, and especially in New York City where almost two thirds of cases have occurred, has aroused international interest[2]: the proportion of patients with MDR tuberculosis had doubled within seven years by the early 1990s so that almost one fifth of tuberculosis cases were MDR tuberculosis.[2] Incorrect treatment or poor compliance with therapy is the underlying cause of MDR tuberculosis—for example, at one hospital in Harlem, almost 90% of patients were lost to follow up.[2] Incorrect treatment selects spontaneous drug resistant mutants of *Mycobacterium tuberculosis* which gradually become the dominant population. Cases remain infectious for longer as standard therapy is ineffective, contributing to the development of outbreaks. Nosocomial MDR tuberculosis outbreaks involving over 300 cases were investigated by the US Centers for Disease Control (CDC) between 1990 and 1992.[3] Almost 90% of patients were coinfected with HIV and within this group there was a high mortality of 80–90% with death occurring between four and 16 weeks after diagnosis. Over 100 health care workers became infected, 17 developed active disease and seven died.

Molecular epidemiological techniques have been used to establish risk factors for acquisition of MDR tuberculosis and the probability of recent transmission rather than reactivation. Alland *et al*[4] demonstrated that approximately two thirds of drug resistant cases resulted from recent transmission and that as many as 30–40% of tuberculosis cases in their study population in the Bronx were recently acquired. Risk factors for MDR tuberculosis included co-infection with HIV, prior tuberculosis therapy, Hispanic ethnicity, poverty, and recent immigration. Similar outbreaks in Europe have now been reported in London,[5] Paris, Lisbon, Madrid, and Milan with most cases occurring in HIV positive patients.

Table 1 summarises the number of drug resistant and MDR tuberculosis isolates received and identified by the Public Health Laboratory Service (PHLS) Regional Centre for Mycobacteriology (now the PHLS Mycobacterium Reference Unit) from 1981 to 1994. Over 95% of mycobacterial cultures in southern England are evaluated by the Centre.

In England and Wales, between 1982 and 1991, MDR tuberculosis was found in 0.6% of laboratory isolates received by the PHLS Mycobacterium Reference Unit and the Regional Centres for Mycobacteriology.[6] Currently the PHLS and Reference Centres in Scotland and Northern Ireland monitor about 50 MDR tuberculosis cases each year in the UK, which represents about 1–2% of laboratory isolates.

The extent of MDR tuberculosis worldwide is difficult to estimate as, with certain exceptions, systematic data are not available. Drug resistance has certainly been increasing worldwide but much of the data are anecdotal and

Table 1 Drug resistant cases of Mycobacterium tuberculosis *identified at the Regional Centre for Microbiology from 1981 to 1994*

Year	Single drug resistance			MDR tuberculosis (isoniazid and rifampicin)	Total M tuberculosis cases	Total drug resistant*	Per cent drug resistant
	Isoniazid	Rifampicin	Pyrazinamide				
1981	40 (2.7%)	1 (0.07%)	0 (0%)	1 (0.07%)	1477	86	5.8%
1982	30 (2.3%)	0 (0%)	0 (0%)	1 (0.08%)	1298	63	4.9%
1983	28 (2.3%)	3 (0.25%)	4 (0.33%)	5 (0.41%)	1214	88	7.2%
1984	18 (1.5%)	1 (0.8%)	13 (1.0%)	1 (1.0%)	1183	64	5.4%
1985	22 (1.8%)	1 (0.08%)	5 (0.4%)	2 (0.16%)	1236	68	5.5%
1986	30 (2.5%)	0 (0%)	0 (0%)	1 (0.8%)	1206	72	6.0%
1987	25 (2.2%)	0 (0%)	1 (0.9%)	3 (0.26%)	1148	60	5.2%
1988	24 (2.3%)	1 (0.1%)	5 (0.49%)	1 (0.1%)	1028	62	6.0%
1989	30 (2.8%)	1 (0.9%)	5 (0.46%)	2 (0.18%)	1088	86	7.9%
1990	21 (1.8%)	1 (0.08%)	4 (0.34%)	0 (0%)	1178	84	7.1%
1991	46 (3.7%)	4 (0.32%)	1 (0.08%)	0 (0%)	1250	99	7.9%
1992	41 (3.3%)	0 (0%)	3 (0.25%)	2 (0.16%)	1245	94	7.6%
1993	40 (3.4%)	2 (0.17%)	3 (0.26%)	2 (0.17%)	1161	101	8.7%
1994	33 (2.8%)	3 (0.26%)	4 (0.34%)	4 (0.34%)	1169	95	8.1%
Total	428 (2.5%)	18 (0.11%)	48 (0.28%)	25 (0.14%)	16881	1122	6.6%

*Total drug resistance includes strains resistant to streptomycin and strains resistant to multiple drugs other than rifampicin and isoniazid.

extrapolation of data from high-risk communities nationally has been misleading.[7] An ongoing initiative, the WHO Global Surveillance of Drug Resistance in Tuberculosis will produce, over the next few months, a more realistic assessment of resistance in many developing countries to complement initiatives in the developed world.

Mutations in genes associated with isoniazid, rifampicin, streptomycin, and ciprofloxacin resistance in most, but not all strains, have been identified, offering the possibility of rapid molecular rests for drug resistance in the next few years.[8 9] Nevertheless, whereas most rifampicin resistance is associated with mutations in a single small region of the gene encoding the beta subunit of the DNA dependent RNA polymerase, isoniazid resistance is associated with multiple genes. MDR tuberculosis is acquired through the stepwise selection of mutants in poorly compliant patients and resistance is chromosomally rather than plasmid mediated in tuberculosis.[9]

Treating MDR tuberculosis requires prolonged hospitalisation, the use of more toxic second line therapy and perhaps adjunct surgery. Treatment is certainly expensive and 'salvage' therapy has been estimated to cost $180 000 per patient in the USA.[10] Nevertheless, recent evidence has shown that even in HIV positive patients death is not inevitable. In one study in HIV negative patients in New York City, 24 (96%) of 25 patients showed a clinical response to individualised treatment[11]; a further study of 38 cases in which 34 (89%) were also HIV positive produced a median survival of 315 days.[12]

Successful therapy is associated with early diagnosis, treatment with at least three agents to which the isolate is susceptible and ensuring compliance through—for example, the use of directly observed therapy (DOT).[13] MDR tuberculosis is a serious clinical, diagnostic and public health problem but it is, with appropriate resources and expertise, a solvable one.

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Rights of possession in human corpses

A recent case, Dobson and Another *v* North Tyneside Health Authority and Another, raised the question of whether the next of kin had possessory rights in cadaveric specimens.[1] A postmortem had been performed at the coroner's request and part of the brain (including brain tumour) of the deceased had been fixed in paraffin wax. Having been preserved for the duration required by the Coroners Rules (S1 1984 No 552), the brain was disposed of by the hospital. The brain was required by the plaintiffs, the administratrix of the estate and the son of the deceased, as evidence in a civil litigation case against North Tyneside Health Authority for alleged negligence in the treatment of the deceased. The Court of Appeal upheld an order that there could be no claim against the hospital which had stored the brain after the necropsy for subsequently disposing of it. The next of kin had not become personal representatives (administrators) at the time when the alleged wrongful interference with their possessory rights in the corpse had taken place. The Court of Appeal held that as next of kin they had no such rights.

In England, there is 'no property in a corpse' although there is increasing academic support for some proprietary rights.[2] It is sometimes suggested that the earliest authority is Haynes's case (1614)[3] determining the inability of a corpse to have proprietary rights in burial sheets, which was misinterpreted by commentators as meaning that a corpse was not capable of being property but was under ecclesiastical jurisdiction. Haynes was punished for stealing the shrouds. The earliest direct English authority appears to be Exelby *v* Handyside (unreported; preserved Siamese twins could not be property).[4] In the eighteenth and nineteenth centuries, the practice of exhumation of buried corpses[5] led to several cases reaching the courts. In 1723–4, a clause was suggested (but later withdrawn) in a Parliamentary Bill providing that bodies of executed persons in the counties of Cambridge and Huntingdon should be available for anatomical teachings. The supply from body-snatchers or resurrectionists was objected to by the local inhabitants and led to an attack on the Cambridge anatomical school in 1833.[6] In Sharpe's case (1856–7),[7] in which a son removed his mother's remains from a graveyard the 'no property' rule was upheld and the defendant charged for trespass to land. In Williams *v* Williams (1882),[8] in which a friend of the deceased disinterred the body and sued the executors to recover the costs in accordance to a codicil in the deceased's will, it was stated

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Notes