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Isoniazid-resistant tuberculosis in Birmingham, United Kingdom, 1999–2010

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Summary

Background: There have been few studies on risk factors and treatment outcomes of isoniazid (H)-resistant tuberculosis (TB), and optimal treatment regimens are debated.
Aim: To identify risk factors for H-resistant TB, describe treatment regimens and compare these to national guidelines and describe short-term outcomes of H-resistant TB in Birmingham, UK.
Design: Retrospective case series.
Methods: Cases of H-resistant tuberculosis in Birmingham between January 1999 and December 2010 ($n = 89$) were compared with drug-susceptible cases ($n = 2497$). Treatment regimens and outcomes at 12 months from diagnosis were evaluated by case note review.
Results: No independent predictors for H-resistant TB were found. For 76/89 (85%) patients with full treatment details available, median treatment duration was 11 months (interquartile range 9–12 months). Only 27/72 (38%) patients with H-mono-resistance were treated in line with national guidelines. A further 14/72 (19%) were treated according to other recognized guidelines. Overall treatment success was 75/89 (84%). Treatment failure occurred in 6/89 (7%) patients, all developed multi-drug resistance. Poor adherence was documented in these patients and use of a non-standard regimen in one patient was not thought to have contributed to treatment failure.
Conclusions: No discriminating risk factors for early detection of H-resistant TB were found. Treatment regimens in clinical practice were highly varied. H-resistance can drive MDR-TB when there is evidence or suspicion of poor adherence. A low threshold for enhanced case management with directly observed therapy is warranted in this group.

Introduction

Isoniazid (H)-resistance is the commonest drug resistance encountered in tuberculosis (TB) cases in the United Kingdom (UK), involving 6.8% of new isolates in 2012.[1] H-resistance in the UK is associated with being non-UK born, previous TB treatment and a history of homelessness.[1]

The optimal regimen and duration of treatment for H-resistant TB has not been well established. Current treatment guidelines are based on one randomized controlled trial in Kenya[2] and *post hoc* analysis of the British Medical Research Council (MRC) clinical trials from the 1970s and 1980s.[3] The Kenyan trial found low failure (<1%) and relapse rates (3–4%) in H-monoresistant cases when treated with 6 or 9 months of rifampicin (R) and ethambutol (E) in the continuation phase, with an initial phase that included both pyrazinamide (Z) and streptomycin (S). Results from the British MRC trials also found low failure rates (2%) when H-resistant (and/or S resistant) cases were treated with a 6-month regimen containing 4–5 drugs including R.

Recent evaluation of available treatment guidelines for H-resistant TB report good outcomes compared with drug-susceptible TB,[4] but others report a

high failure rate and considerable risk of multi-drug resistant TB (MDR-TB).[5,6] We conducted an audit to retrospectively identify risk factors for H-resistant TB and describe treatment regimens and short-term outcomes of H-resistant TB in Birmingham, UK, a city with a high incidence of TB (51 per 100 000 in 2009).[7]

Methods

Cases of culture-confirmed, H-resistant TB diagnosed between 1 January 1999 and 31 December 2010 were identified from a prospectively maintained, electronic database of mandatory notifications of TB cases from all hospitals treating TB in the city of Birmingham and urban borough of Solihull (estimated population 1.24 million in 2010).[8] Cases were excluded if there was concomitant R resistance, i.e. multi-drug resistant (MDR) or if H-resistance developed during treatment. Cases with documented susceptibility to all four first line drugs (H, R, Z and E) in the same time period were used as a comparison cohort. Drug susceptibility testing was performed at Public Health England Regional Centre for Mycobacteriology, Birmingham using the resistance ratio or proportion method.[9]

Demographic and clinical characteristics for H-resistant and fully susceptible cases were extracted from the electronic database. Detailed information on treatment regimens and outcomes for the H-resistant cohort were examined from the medical and nursing case notes held at the Birmingham Chest Clinic. Pulmonary TB was defined as TB affecting the lungs, pleural cavity, mediastinal lymph nodes or larynx.[11] For H-resistant pulmonary cases, disease severity was graded as minimal (no cavities), moderate (some cavities) and advanced (multiple cavities) according to the extent of radiographic disease[10] available from formal reports. Regimens were considered in line with national guidelines if patients received at least RZE for a minimum of 2 months followed by at least RE for a minimum of 12 months.[11]

Short-term treatment outcomes at 12 months from diagnosis were adapted from the World Health Organization (WHO).[12] Patients were considered successfully treated if they completed a full course of prescribed treatment and had documented sputum culture conversion (for sputum culture-positive cases) or were discharged by their attending physician. Treatment stopped was recorded if the attending physician stopped treatment for any reason. Treatment failed if a case was smear- or culture-positive at month 5 or later during treatment. Patients were lost to follow-up if treatment was interrupted for two consecutive months or more. Death from any cause during treatment was recorded. The electronic database was searched for patients with a second episode of TB up to 31 December 2013.

The audit was approved by the Heart of England NHS Foundation Trust Audit and Governance Directorate.

Statistical analysis was conducted in *R* (R Core Team, 2012). Dichotomous variables were analysed by contingency analysis and continuous variables by the Mann-Whitney *U* test. Predictor variables for H-resistance at a significance level of $P < 0.2$ were included in a logistic regression model.

Results

There were 4608 notified TB cases in Birmingham during the audit period, of which 2630 (57%) were culture-confirmed (Figure 1). Susceptibility to all four first line drugs was documented in 2497 cases (95%). Eighty-nine (3%) were H-resistant, with 85 cases (94%) having no additional resistance to any first line drug, i.e. H-monoresistant. Of the remaining 44 culture-confirmed cases, 28 were MDR, 12 were Z monoresistant, 3 were R monoresistant and 1 was E monoresistant. Over the 12-year study period, the proportion of H-resistance varied between 1 and 6% (Figure 2).

Univariable analysis of a number of baseline characteristics was performed to determine whether any clinical factors at presentation could be used to predict H-resistance (Table 1). In our cohort, over half of both H-resistant and fully susceptible TB cases were in those of Indian or Pakistani ethnicity. Most factors including age, sex, ethnicity, history of previous TB, whether pulmonary or non-pulmonary TB and HIV status were not statistically different. The proportion of patients born outside the UK was higher in H-resistant cases compared with fully sensitive cases (80 vs. 70%, $P = 0.046$). More H-resistant pulmonary cases were sputum smear-positive (66 vs. 50%, $P = 0.02$). However, on multivariable analysis no clinical factors were independently associated with H-resistance.

Treatment regimens could be fully evaluated for 76/89 (85%) of patients (Figure 1; Table 2). All treatment was given daily without directly observed therapy. The median treatment duration was 11 months (interquartile range, IQR 9–12 months). Only 27/72 (38%) patients with H-monoresistance were treated in line with national guidelines (Figure 1). RE was the most common regimen in the continuation phase (34/76, 45%) with a median treatment time of 12 months (IQR 10–12 months) (Table 2). In

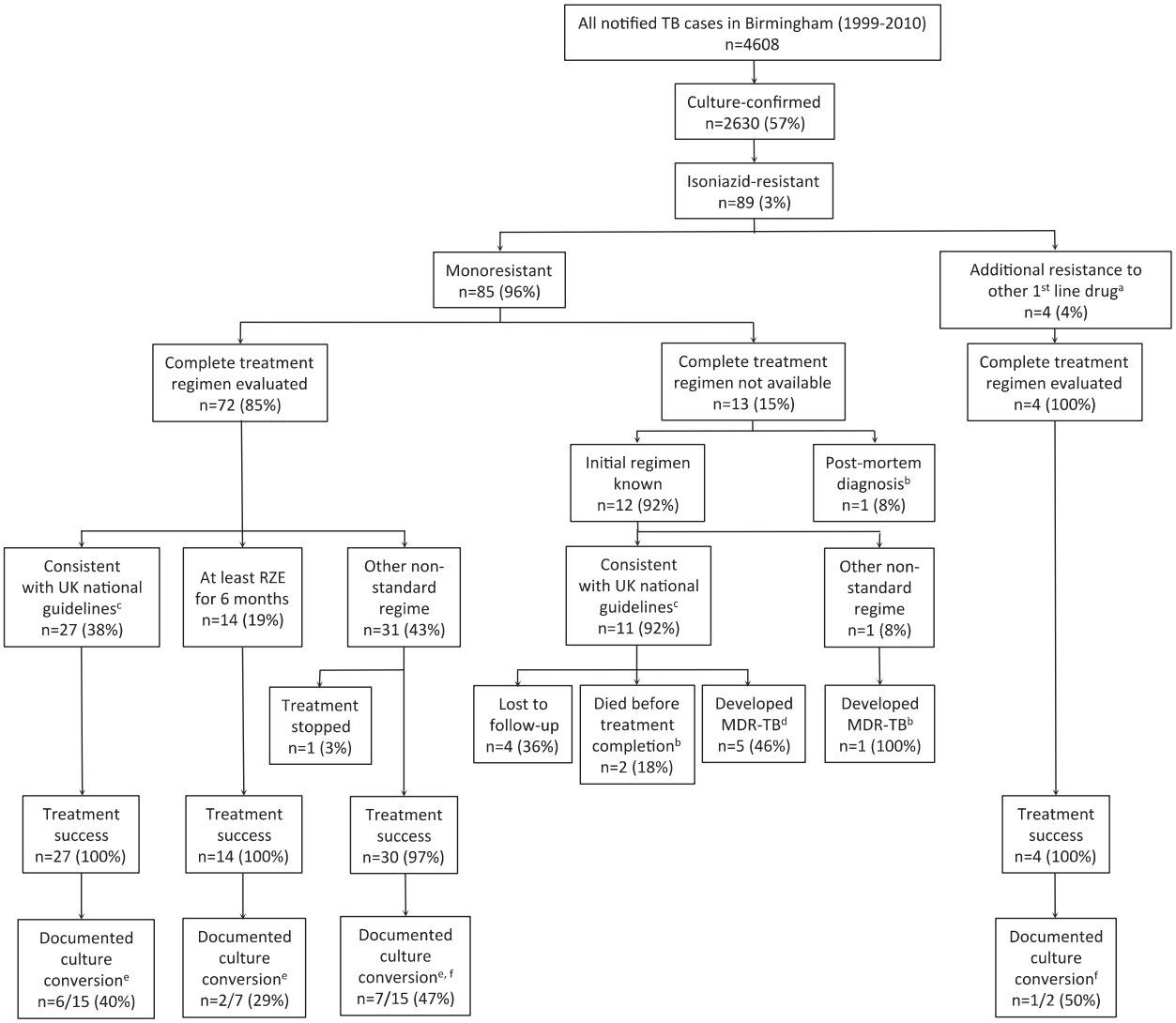

Figure 1. Management and outcomes at 12 months from diagnosis for 89 isoniazid-resistant TB cases in Birmingham, 1999–2010. R, rifampicin; Z, pyrazinamide; E, ethambutol; MDR, multi-drug resistant. Percentages were calculated using the previous box as the denominator, except where otherwise stated. [a]3 patients had additional resistance to E, one had additional resistance to Z. [b]1 patient died of TB. [c]At least RZE for a minimum of 2 months followed by at least RE for a minimum of 12 months. [d]2 patients died of TB, 2 patients were lost to follow-up and 1 patient was still on treatment. [e]Conversion after month 5 of treatment or later. The denominator used was number of sputum culture-positive specimens obtained non-invasively before treatment. [f]2 patients were smear- and culture- positive after month 2 of treatment.

patients that received RE for less than 10 months in the continuation phase, none had received more than 2 months of a quinolone in the intensive phase.

A considerable proportion of patients (25/76, 33%) tolerated Z throughout their treatment regimen (median treatment duration 9 months, IQR 9–12 months) (Table 2). Concomitant RE administration with Z was found in only 14/72 (19%) of patients with H-monoresistance (Figure 1). Twenty of 76 patients with full treatment evaluation (26%) were additionally treated with a quinolone either in the intensive phase (9 patients), the continuation phase (4 patients) or throughout treatment (7 patients) (Table 2). Eleven of these patients had pulmonary disease, with 10 patients having minimal disease and 1 patient having moderate disease. A further four patients had peripheral lymph node disease and the remainder had bone and joint or soft tissue disease. Quinolone use was not statistically associated with pulmonary disease (proportion of pulmonary cases receiving quinolone vs. no quinolone, 55 vs. 60%, $P = 0.856$).

For 13/89 (15%) of patients, complete treatment regimens could not be fully assessed (Figure 1). Of the 12 patients started on treatment, 11 started with quadruple therapy with 3 patients additionally receiving a quinolone in the intensive phase due to moderate or advanced pulmonary disease.

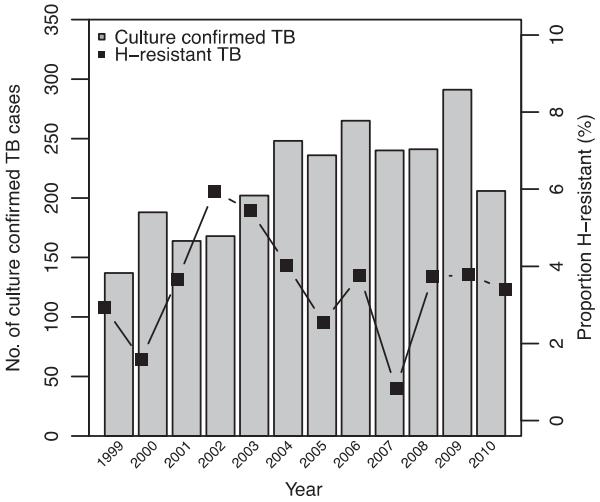

Figure 2. Isoniazid-resistant TB cases in Birmingham, 1999–2010.

Seven patients were either lost to follow-up or died before treatment completion. In the other six patients, regimens were complex due to adherence problems with subsequent development of MDR-TB. One of these patients was treated with RHZ without E at the start of treatment, but poor treatment compliance was a greater factor in development of MDR rather than the non-standard treatment regimen.

Treatment success was achieved in a total of 75/89 (84%) patients (Figure 1). Only 16/75 (21%) of successfully treated patients had documented culture conversion after month 5 of treatment or later. Even after accounting for pragmatic difficulties in cases where a repeat culture specimen required invasive procedures, the documented culture conversion rate remained low (16/39, 41%) (Figure 1). Six cases (7%) failed treatment. All were poorly adherent to treatment and all developed MDR-TB, with 3/6 patients known to have eventually died of TB.

Table 1 Baseline characteristics and univariable analysis of factors associated with isoniazid-resistance

Characteristic	H-resistant ($n = 89$)	Fully sensitive ($n = 2497$)	P
Male	41 (46)	1346 (54)	0.15
Age, median years (IQR)	30.8 (25.5–41.8)	35.4 (25.5–54.7)	0.054[a]
Ethnic group			
White	8 (9)	354 (14)	0.40
Pakistani	30 (34)	840 (34)	
Indian	20 (22)	473 (19)	
Black African	18 (20)	415 (17)	
Black Caribbean	3 (3)	184 (7)	
Other	10 (11)	231 (9)	
Place of birth			
UK	18 (20)	751 (30)	0.046
Non-UK	71 (80)	1746 (70)	
Indian subcontinent	45 (51)	1124 (64)	
Africa (except Northern Africa)	18 (20)	401 (23)	
Middle East and Northern Africa[b]	4 (5)	57 (3)	
Caribbean and Latin America	0	56 (3)	
Europe	1 (1)	48 (3)	
Southeast Asia and Far East	2 (2)	45 (3)	
Not known	1 (1)	15 (<1)	
Clinical characteristics			
Previous TB	7 (8)	123 (5)	0.21
Pulmonary TB[c]	56 (63)[d]	1776 (71)	0.09
Sputum smear positive	37 (66)	883 (50)	0.02
HIV positive	1 (1)	20 (<1)	0.74

Notes: Data are no. (%) of patients, unless indicated otherwise. Dichotomized data were assessed by contingency analysis. H, isoniazid; IQR, interquartile range.

[a]Mann–Whitney *U* test.

[b]Northern African countries were Sudan, Egypt, Libya and Algeria.

[c]Of the 33 non-pulmonary cases, 18 had peripheral lymph node disease, 12 had bone and joint disease, 2 had soft tissue disease and 1 had intestinal disease.

[d]Of the pulmonary cases, 43 patients had minimal disease, 5 had moderate disease and 4 had advanced disease. Disease extent was unknown for four patients.

Table 2 Treatment regimens, duration of treatment and known relapses in 76 isoniazid-resistant TB patients with complete treatment regimens available

Minimum duration of treatment	Intensive phase		Continuation phase	
	Drug regimen	No. of patients (no. with H in regimen)	Drug regimen	No. of patients (no. with H in regimen)
6 months, *n* = 12	RZ(H)	4 (4)	R(H)	5 (5)
	RZE(H)	8 (7)	RZ(H)	3 (1)
			RE	1
			RZE(H)	2 (1)
			RCip	1
9 months, *n* = 26	E(H)	1 (1)	E(H)	1 (1)
	RZ(H)	1 (1)	R(H)	2 (2)
	RZClari	1	RE	8[a]
	RZE(H)	17 (15)	RZ	1
	RZEMox	3	RZE(H)	11 (3)
	RZECip(H)	2 (1)	RZEMox	1
	RZEClari	1	REClari	1
			RClari	1
12 months, *n* = 38	RE(H)	1 (1)[b]	RE(H)	25 (2)[b,c]
	RZE(H)	25 (20)[c]	REMox	2
	RZEMox	5	REClariCip	1
	RZCip(H)	2 (1)	RZ(H)	2 (1)
	RZMox	1	RZMox	1
	REMox	1	RZCip	1
	REClari	1	RZE	1
	ZCip	1[d]	RZEClari(H)	1 (1)
	EMox	1	RMox	2
			ZCip	1[d]
			EMox	1

Notes All treatment was given daily without routine use of directly observed therapy. R, rifampicin; H, isoniazid; Z, pyrazinamide; E, ethambutol; Cip, ciprofloxacin; Mox, moxifloxacin; Clari, clarithromycin; MDR, multi-drug resistance
[a]These patients received quadruple therapy in the intensive phase and no relapses are known to have occurred.
[b]One patient with pulmonary TB had a culture-negative, clinical relapse 3 years later. The patient did not have pyrazinamide in the intensive phase and the continuation phase was 16 months.
[c]One patient with peripheral lymph node TB had a culture-negative, clinical relapse 8 years after treatment completion.
[d]This patient with peripheral lymph node TB had a culture-confirmed relapse 2 years after treatment completion. Relapse was confirmed by 15-loci mycobacterial interspersed repetitive unit-variable number tandem repeats (MIRU-VNTR).

There were 3/89 (3%) TB deaths within 12 months diagnosis, of which 2 were TB-related. One was a pulmonary case diagnosed at post-mortem and the other was a patient with TB meningitis. Treatment was stopped in 1/89 (1%) patient and 4/89 (5%) patients were lost to follow-up. Median follow-up time from treatment completion in our cohort was only 3 months (range 0.5–108 months). However, 3/75 (4%) patients who were successfully treated at 12 months were known to have a further treatment episode for TB 2 to 8 years later (Table 2).

Discussion

The overall incidence of H-resistant TB in Birmingham remains low at 3% compared with 7% for England as a whole. This figure is skewed by an outbreak of H-monoresistant TB in London.[13] Most patients did not give a history of previous TB and the majority had primary H-resistance. No H-resistant clusters are known to have occurred in Birmingham based on epidemiological data or strain typing by 15-loci mycobacterial interspersed repetitive unit–variable number tandem repeats (MIRU-VNTR) available from 2003 onwards. The increased proportion of H-resistant TB between 2001 and 2003 also appears to be due to sporadic cases. Two of six cases with available strain typing during this period had identical 15 loci MIRU-VNTR but no definite epidemiological links could be found. No other epidemiological links could be detected between the other cases. This suggests that

most patients in Birmingham had acquired TB abroad, where rates of H-resistance may be higher.

We did not find any predictive factors for H-resistant TB. Several studies have identified different clinical risk factors for H-resistant TB including previous TB treatment[4,14] and younger age groups.[15,16] In the London outbreak risk factors included being younger, UK born, of white or Black Caribbean ethnicity and having social risk factors such as being a prisoner at the time of diagnosis, drug dealer, sex worker or unemployed.[13] This risk profile is not evident in our cohort. One limitation of our study is the small sample size. However the difficulty in predicting which cases will have any drug resistance, including multi-drug resistance resonates with our own clinical experience. The routine use of rapid diagnostic tests for drug resistance in low-incidence, high-income settings still carries cost implications and is unlikely to be implemented. It is anticipated that whole-genome sequencing will replace MIRU-VNTR in the future and thus rapid detection of resistance will be possible.[17] In H-monoresistance prediction of H-resistant before starting treatment is less important as all patients should routinely start with quadruple therapy.

Treatment regimens and durations were highly heterogeneous. This is well-recognized in routine clinical practice[18] and may reflect the debate on optimal treatment regimes for H-monoresistant TB. Less than half were treated in accordance with UK national guidelines, which recommend continuing R and E for 12 months, with Z in the initial 2 months.[11] It has been suggested that a 9-month regimen may be adequate,[19] in our patients treated for this duration no relapses have been referred back to our centre but no firm conclusions on relapse rates with any regimen can be drawn as migration out of area cannot be accounted for with our study design. Individualized therapy based on drug toxicity and drug susceptibility testing may have contributed to the varying regimes, although we did not differentiate between those with high or low level H-resistance in this study. In addition, extensive or cavitary pulmonary disease cases are at higher risk of relapse[20] and this may have contributed to use of greater number of active drugs in the initial phase in this group. This strategy, as well as longer duration of R use, S use and daily therapy initially was associated with lower rates of failure, relapse and acquired drug resistance in a recent meta-analysis of patients with previous a history of previous treatment or monoresistance to H.[21] However, until further evidence from randomized-controlled trials are available, we recommend that national guidelines are followed and use of second-line drugs limited to patients with intolerance to first-line agents or when first-line regimen failure is suspected based on serial culture results.

Treatment success rates of H-resistant cohorts have been reported from California (95%),[4] Texas (92%),[18] South Korea (92%),[22] Denmark (80%),[23] Georgia (71%),[6] Western Cape Province, South Africa (65%)[5] and London (65%).[13] Our short-term treatment success rate of 84% lies somewhere in between and is comparable to national short-term outcomes for drug-sensitive TB.[1] Although non-standard regimens did not contribute to the development of poor outcomes directly, the large variability in prescribed treatment is concerning and our study is the first to report the lack of standardization within an unselected UK cohort. Poor practice was evident in some cases whereby the attending physician was not aware of the presence of drug resistance. Furthermore, the use of clarithromycin in treatment regimens could not be justified. We have addressed this within our organization through the audit process. Standardized treatment protocols have been implemented and will be reaudited. Our study also highlights again the risk of progression to MDR-TB and death in patients with poor compliance. This underscores the need for continued vigilance in this group of patients with carefully tailored and robust drug regimens, the use of directly observed therapy and attention to social problems that may be barriers to an individual's compliance. Our findings have provided the impetus for resource re-allocation so that all H-monoresistant TB cases in Birmingham are now under enhanced case management and receive directly observed therapy. While individual patient behavior can be challenging, all cases that develop resistance on treatment are also subject to root cause analysis so that recurring organizational failures can be prevented.

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