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NICE guidelines and the length of inpatient stay for tuberculosis

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ABSTRACT In response to recently published NICE guidelines on the management of patients with MTB, we conducted a retrospective study of adult patients admitted to a large teaching hospital with a confirmed diagnosis of MTB between January 2000 and December 2005. Fifty-five patients had pulmonary infection, of whom 49 remained in negative pressure rooms throughout admission and 21 had sputum microscopy positive for acid-fast bacilli. The mean time taken to return smear results was 26 hours, cultures 36·8 days and susceptibility testing 64·0 days. The mean length of stay for MDR-TB patients was 83·5 days compared with 39·9 days for non-MDR-TB patients. HIV-positive patients did not have prolonged admissions whereas solid organ transplant recipients did ($p<0·0001$). The use of automated liquid culture (51%) and rpoB gene (42%) and HIV testing (43%) fell short of suggested standards yet this did not affect length of stay. The study reflected rising numbers of cases of TB nationally with implications for provision of negative pressure facilities.

KEYWORDS Tuberculosis, inpatients, NICE guidelines, isolation

LIST OF ABBREVIATIONS Acid fast bacilli (AFB), American Thoracic Society (ATS), British Thoracic Society (BTS), Human Immunodeficiency Virus (HIV) multidrug-resistant tuberculosis (MDR-TB), Mycobacterial Reference Unit (MRU), *Mycobacterium tuberculosis* (MTB), National Institute of Health and Clinical Excellence (NICE), patient administration system (PAS), polymerase chain reaction (PCR), RNA polymerase B (rpoB), tuberculosis (TB).

DECLARATION OF INTERESTS No conflict of interests declared.

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INTRODUCTION

In the past two decades the UK has seen a rise in MTB infections. The incidence is now approximately 14·7 per 100,000 people per year, and is higher in large cities and areas with significant numbers of immigrants from high burden countries.[1] Of similar concern is the global rise in incidence of MDR-TB, defined as resistance to both isoniazid and rifampicin, which has been modestly reflected in the UK.[2] The response to this problem in resource rich countries includes improving vaccine programmes, screening immigrants from high burden countries and developing services for the rapid diagnosis of new cases as they occur.[3] This last strategy has placed a particular demand on laboratory services and clinicians. The availability of rapid diagnostic techniques such as automated liquid culture systems and the rpoB gene test (for rifampicin resistance) can facilitate the early detection of disease and control the spread of drug resistance.[4]

In 2000, the BTS published updated guidelines for the diagnosis and management of patients with MTB.[5] The ATS have also produced guidelines jointly with the Centres for Disease Control and Prevention, and the Infectious Diseases Society of America.[3] Revised criteria for turnaround times for laboratory tests and recommendations for the use of molecular tests for diagnosis of MTB in the UK have also been published.[4] More recently, NICE have produced guidelines for the diagnosis and management of MTB.[6] The latter are of particular interest for their recommendations on the use of automated liquid culture and molecular testing.

We conducted a retrospective study of patients with culture positive MTB infection in Addenbrooke's Hospital with the following aims:

1 To assess the number of inpatients with MTB over a six-year period from January 2000 to December 2005.
2 To assess how well the use of negative pressure facilities, automated liquid culture and rpoB gene

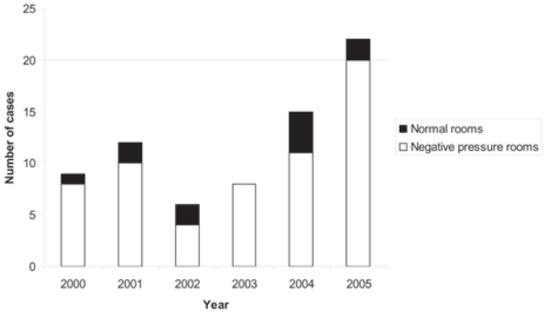

FIGURE 1 Number of cases per year and the use of negative pressure rooms.

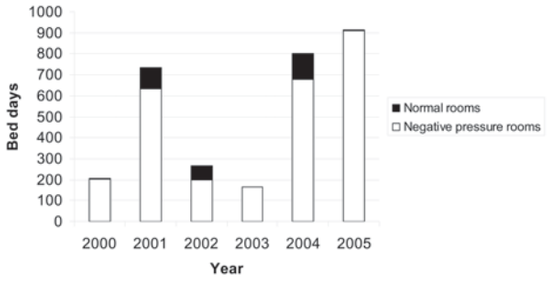

FIGURE 2 Bed days used by TB patients according to facility used.

testing during this period met current guidelines.[5,6]

3 To determine whether the following had an effect on the length of stay of TB patients:
   a Speed of return of results from microbiology.
   b Immunosuppression.
   c Infection with a multidrug-resistant strain of TB.

Audit standards were set using the BTS and NICE guidelines and standards for laboratory test turnaround times (not stipulated by the BTS or NICE) were adopted from published guidance.[4–6]

METHODS

Addenbrooke's Hospital, Cambridge is a teaching hospital with approximately 1,100 beds and almost 62,000 in-patient episodes per year. It is a tertiary referral centre for an area of England with a low incidence of TB.[1] We performed a retrospective study of all adult patients with a positive culture result for MTB complex on the hospital microbiology database from January 2000 to December 2005 and all patients with a histological diagnosis of MTB complex from January 2004 to December 2005. Approval for the study was obtained from the hospital Audit Committee. Patients with environmental mycobacterial infection and patients who remained in hospital for less than 24 hours were excluded from the study. Patients below the age of 18 years were also excluded because this group are managed by paediatricians in separate isolation facilities. A single episode of infection was considered as one case, irrespective of the number of admissions for that individual.

Data were obtained from the laboratory computer and PAS and entered onto a standard database. This included admission and discharge dates, date of birth, sex, admitting team, ward, use of negative pressure rooms, type of samples, sputum AFB smear results, turnaround time for smear, culture and susceptibility results, use of liquid culture and rpoB gene testing, immune status and outcome. Details of patient medications were obtained from PAS and the pharmacy computer system. Patients without a serological test for HIV were excluded when comparing immunocompetent patients with HIV-positive patients.

Microscopy for AFB was performed on-site, together with culture on Lowenstein-Jensen slopes for all specimens. If a decision was made to perform liquid culture, the specimen would be sent to a regional laboratory with the appropriate facilities. Susceptibility tests and, when requested, PCR and rpoB gene tests were performed at the MRU, Health Protection Agency, Whitechapel, London.

RESULTS

Seventy-five patients infected with MTB were admitted between January 2000 and December 2005. Twenty patients had non-pulmonary disease and 55 had pulmonary disease, of whom 21 were sputum smear-positive. Four inpatients (5%) died whilst being treated. Patients infected with MTB used a total of 2,785 bed days in negative pressure rooms and 301 bed days on open wards. The mean length of stay for patients in negative pressure rooms was 43·5 days (standard deviation 78·2 days) and for those on open wards was 27·4 days (standard deviation 32·8 days). Figures 1 and 2 show the number of TB cases and the number of bed days they used per year in each type of facility.

Ninety-one percent of pulmonary TB patients were admitted to negative pressure facilities until their sputum smear status was known. Five patients with pulmonary TB were admitted to side rooms on open wards that would have also accommodated immunosuppressed patients. All pulmonary TB patients diagnosed as sputum smear-positive as well as all HIV-positive TB patients and all those with MDR-TB remained in negative pressure facilities for the duration of their admission.

Fifty one percent of patients (38 out of 75) had samples sent for automated liquid culture and the rpoB gene status of isolates was known for 42% of patients (31 out of 75). Seventy one percent of sputum-smear positive patients (15 out of 21) had samples sent for rpoB gene testing. For HIV-positive patients (a known risk factor for MDR-TB)[7] 57% of patients had samples tested for the rpoB gene. Two patients had MDR-TB; one patient was diagnosed by both rpoB gene and susceptibility testing but the other patient was diagnosed only by susceptibility testing (rpoB testing was not done).

With regard to turnaround times for laboratory tests, the mean time to return sputum smear results was 26 hours (standard deviation 27·6 hours) and 76% were returned within the target 24 hours. The mean time to return culture results was 36·8 days (standard deviation 44·6 days) and 22% were returned in the target 21 days. The mean time to return susceptibility results to first-line therapies (isoniazid, rifampicin, ethambutol, pyrazinamide and streptomycin) was 64 days (standard deviation 50·1 days) and 57% were returned in the target 60 days. Whilst these results show that suggested standards[4] set for turnaround times were not achieved in a substantial proportion of cases, the time to return smear, culture and susceptibility results had no effect on a patient's length of stay.

There were twelve patients (16%) with isolates resistant to at least one first-line drug. Four patients had isolates resistant to streptomycin, two each had isolates resistant to isoniazid or pyrazinamide and one patient had an isolate resistant to ethambutol. Two patients had MDR-TB isolates and one patient had an isolate resistant to the three first line agents ethambutol, pyrazinamide and rifampicin. The mean length of stay for the twelve patients with resistance to at least one first-line drug was slightly longer (47 days, standard deviation 29·3 days) but not significantly different to those with fully susceptible strains (40 days, standard deviation 81·2 days, P = 0·77). The two MDR-TB cases had a mean length of stay (83·5 days, standard deviation 34·6 days) longer than patients with non-MDR-TB (40·2 days, standard deviation 75·6 days), but this difference was not statistically significant (P = 0·42). Drug regimens were modified promptly following susceptibility results in line with current treatment guidelines.[6] The full drug susceptibility results for isolates from three patients were not known because they were either diagnosed at a different hospital or had a histological diagnosis.

Twenty-one patients were deemed to be immunosuppressed. Of these, 14 patients had a positive HIV test result, 5 patients were taking some form of immunosuppressive medication and 2 patients had had a previous solid organ transplant. The hospital database had HIV test results recorded for 43% of patients and within this group there was no significant difference in the mean length of stay between HIV-positive (30 days, standard deviation 16·9 days) and HIV-negative patients (49·6 days, standard deviation 87·4 days), P = 0·3. The mean length of stay for patients on immunosuppressive medication (40·2 days, standard deviation 41·7 days) did not differ significantly from immunocompetent patients (42·4 days, standard deviation 84·9 days), P = 0·9. However, patients with solid organ transplants spent significantly longer in hospital than all other groups (89 days (standard deviation 2·8 days), P <0·0001 (see Figure 3).

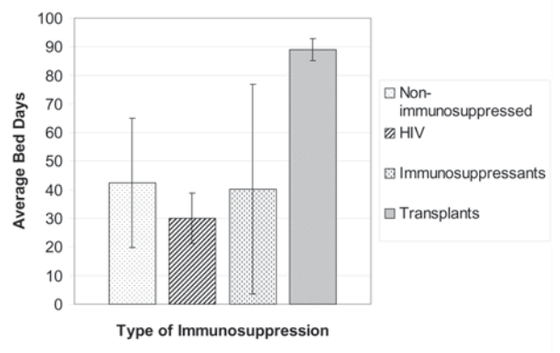

FIGURE 3 Average length of stay (in days) of TB patients categorised by immune status with 95% confidence intervals.

DISCUSSION

Our study showed a year-by-year increase in the number of admissions for MTB from 2002 onwards and a less consistent rise in the number of bed days used by these patients. There are no previous studies on the incidence of MTB among hospital inpatients for comparison, but previously published data on average length of stay showed variation depending on geographical location.[8–10] Even in this relatively low prevalence area, these data predict a rising pressure on the limited availability of negative pressure rooms in a large Trust and impose an obligation for strategic planning within large Health regions for provision of these facilities.

Whilst patients were managed in accordance with the guidelines available during the study period, certain practices would not have attained the standards set by the new NICE guidance. Fifty-one percent of samples were sent for automated liquid culture, rather than all samples as recommended. Analysis of rpoB gene testing for different patient groups suggests an inconsistent risk assessment procedure, for example only 57·1 % of HIV-positive patients (a known risk factor for MDR-TB)[7] had samples tested for the rpoB gene. Whilst there were no data on countrywide practice, one published audit described a London hospital that used automated liquid culture for all samples.[11] Our study suggested that the current methods for determining which samples should be sent for rpoB gene testing required review. There are no relevant studies with which to compare practice.

British Thoracic Society guidelines suggest that all new cases of TB should be tested for HIV. Forty-three percent of patients in our study had their HIV status documented. There are no UK studies for comparison of the level of HIV testing in MTB patients but a study from Saudi Arabia revealed a similar level of testing[12] although another study from the USA achieved a higher percentage of MTB patients tested for HIV.[13]

Turnaround times for culture and susceptibility testing results did not meet published standards[4] and were slower than for other published data in the UK and Europe,[11, 14] but the comparison is complicated by the use of different culture techniques. Despite this, the slower turnaround times had no effect on the length of stay for patients with MTB although it is difficult to exclude that it may have effects on other aspects of inpatient management.[15]

The two patients with MDR-TB stayed an average of 80 days compared to 40 days for patients with susceptible isolates; the difference was not statistically significant probably because of the small number of patients with MDR-TB. The overall outcome for these two patients was not adversely affected by the method of testing for rifampicin resistance as the single MDR-TB patient who had no rpoB gene test was already on second-line antimycobacterial therapy due to suspicion of drug resistance.

Equally, patients on immunosuppressive medication and patients with HIV infection did not stay significantly longer than immunocompetent patients, the latter observation being at odds with other work showing that MTB patients with HIV infection stay longer in hospital.[16] By contrast, patients with solid organ transplants did spend significantly more time in hospital than any other group and this is consistent with other studies that show that transplant patients infected with MTB are at increased risk of morbidity and mortality.[17, 18]

This study was not a comprehensive evaluation of all MTB cases. It was not possible to collect data on patients with a histological diagnosis of MTB before 2004, and we had no data on the management of patients initially suspected of MTB infection but later shown to have negative culture results. The relatively small number of patients involved in the study made analysis susceptible to small number effects; for example there were four patients that between them took up 1,213 bed days. All four were immunocompetent and had fully sensitive isolates and accordingly skewed the length of stay data for that sub-group. Three of the four long-stay cases had disease-related complications; two cases with tuberculous meningitis requiring long term rehabilitation, one with pulmonary tuberculosis and underlying pulmonary fibrosis requiring ventilation, and one case had drug-related toxicity. Whilst the audit identified that the use of rpoB gene testing would not have been consistent with NICE guidelines, it was not possible to identify why individual clinical decisions on the use of this test were made. Furthermore, the NICE guidelines rely on AFB smear status as the main laboratory marker for infectivity based mainly on animal models.[19] Future recommendations on transmissibility may be influenced by emerging research methods on humans.[20] Finally, this study was conducted in a single centre with a specific referral population.

The study results were supportive of a previously planned initiative to introduce a more comprehensive automated liquid culture service locally. Whereas guidelines are designed to provide a framework for a move towards consistent best practice, our findings lead us to recommend establishing local agreements on risk assessment, especially with regard to HIV status and rpoB gene testing. More robust recommendations streamlining national laboratory standards for the diagnosis of tuberculosis are also warranted. Future studies will be required to look into the cost effectiveness of using automated liquid culture for all specimens and the role of molecular tests in the investigation of culture negative cases.

CONCLUSION

The number of patients admitted to hospital for treatment of MTB infection is significant and shows no sign of diminishing. There has been guidance on the use of negative pressure facilities for many years and this was largely adhered to. However, the availability of negative pressure facilities requires urgent strategic forward planning. In the light of new NICE guidelines, discussion is required to establish the correct role for rpoB gene testing, automated liquid culture and HIV testing.

The length of stay for MTB inpatients was not affected by turnaround times for laboratory tests, drug sensitivity of isolates or the immune status of the patient with the exception of patients with solid organ transplants. Further work is required to establish how these patients can be better managed.

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