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Medication errors with antituberculosis therapy in an inpatient, academic setting: forgotten but not gone

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SUMMARY

What is known and objective: **Tuberculosis, an infectious disease caused by the bacteria *Mycobacterium tuberculosis*, has significant public health implications. Despite the decreasing prevalence of tuberculosis cases and the availability of well-established treatment guidelines, errors with antituberculosis medications remain a concern as clinician experience with the infection has waned and the goal of eradicating tuberculosis has remained unfulfilled. Whereas inappropriate use of other anti-infective classes has been extensively studied, the evaluation of medication errors associated with antituberculosis therapy has been limited to a small number of studies conducted more than two decades ago. This study evaluated the prevalence of inpatient medication errors with antituberculosis therapy in patients with suspected or confirmed tuberculosis disease.**

Methods: **All admitted patients treated with at least one antituberculosis medication between July 2010 and June 2013 were evaluated for inclusion in the retrospective study. Multidrug antituberculosis regimens were reviewed for medication errors, which were categorized as dosing errors, drug interactions, omission of therapy and inappropriate continuation of therapy in the presence of drug toxicity. Appropriate management was determined in accordance with the national guidelines for the treatment of tuberculosis, as well as guidelines on the use of antiretroviral agents for patients with both human immunodeficiency virus (HIV) infection and tuberculosis disease. The impact of infectious diseases and pulmonary consultation on the prevalence of medication errors was also examined.**

Results and discussion: **More than half of all study patients (44/72, 61%) experienced at least one medication error associated with antituberculosis therapy. Dosing errors were the most common type of medication error identified and were predominantly related to weight-based dosing. Seven dosing errors were related to drug interactions between rifamycins and antiretroviral therapy in HIV-infected patients. Medication error rates were similar between patients receiving consultation from infectious diseases and/or pulmonary specialties and those without consultation. The large majority of antituberculosis medication errors (56/66 errors, 85%) remained uncorrected during the patient's hospital admission.**

What is new and conclusion: **Medication errors associated with antituberculosis therapy remain a common occurrence in the current clinical practice setting. Greater vigilance when prescribing medications for tuberculosis disease is needed.**

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WHAT IS KNOWN AND OBJECTIVE

Tuberculosis disease is a complex medical condition, requiring the use of a multidrug treatment regimen, prolonged duration of therapy and close monitoring for adverse effects. Although the overall incidence and prevalence of tuberculosis cases are declining in the United States, tuberculosis remains a national concern, particularly in communities with large numbers of foreign-born individuals and other risk groups, such as the homeless, incarcerated and HIV-infected. The spread of tuberculosis has been controlled in part by efforts towards earlier diagnosis and aggressive treatment, and the percentage of patients with tuberculosis receiving a 4-drug treatment regimen with first-line antituberculosis drugs has more than doubled over the past decade.[1] While tuberculosis disease may not be a frequently encountered medical condition, healthcare practitioners must remain knowledgeable and equipped to manage patients with suspected or confirmed active tuberculosis. Appropriate prescribing and use of antituberculosis therapy are essential to optimizing patient outcomes and addressing the persistence of tuberculosis infection.

University Hospital is an urban, academic, tertiary care centre located in Newark, New Jersey, a state with the sixth highest rate of tuberculosis cases in the United States. In 2013, the United States had an aggregate tuberculosis case rate of 3 per 100 000;[1] however, the case rate in Newark during the same year was 10·1 per 100 000.[2] Newark is also home to the Global Tuberculosis Institute, a founding component of the International Center for Public Health focused on the research, practice and teaching of tuberculosis care. Given the availability of clinicians specializing in tuberculosis at the Global Tuberculosis Institute and University Hospital as well as the relatively high rate of tuberculosis cases in the community, one may presume that the institution's practitioners are clinically experienced and comfortable in the management of patients with suspected or confirmed tuberculosis disease.

The definition of a medication error encompasses any preventable event that may occur during the medication use process and potentially (if not actually) lead to inappropriate use or patient harm.[3,4] Studies evaluating the prevalence of medication errors in the inpatient setting have reported rates ranging from 4·8% to 5·3%.[4] Whereas inappropriate use of antibiotic and antiretroviral

therapy has been extensively studied, there are limited data evaluating medication errors associated with tuberculosis therapy.[5–7] This study evaluated the occurrence of medication errors associated with antituberculosis therapy in an inpatient US healthcare setting with a relatively high prevalence of tuberculosis disease.

METHODS

All patients receiving rifampin, isoniazid, pyrazinamide, and/or ethambutol during any admission between July 2010 and June 2013 were retrospectively identified using the institution's pharmacy database. Diagnosis-related coding, notifiable disease records and laboratory testing data were not readily available for the identification of potential study patients and were not expected to identify unique patients outside of the pharmacy database. Those receiving a multidrug regimen for the treatment of suspected or confirmed tuberculosis disease as documented in the medical record were included in the study. Patients receiving therapy for latent tuberculosis infection or continuing outpatient regimens of tuberculosis therapy were excluded. For patients with multiple admissions during the study period, only the first admission was included. Use of antituberculosis medications for other indications, such as *Mycobacterium avium* complex infections or prosthetic orthopaedic infections (in the case of rifampin for *Staphylococcus aureus*), was also not evaluated in this study.

Data on patient demographics, height, weight, HIV status, antituberculosis medication regimens (number of agents, dosing, interactions with other medications), laboratory values over the hospital course and use of infectious diseases and pulmonary consultation were collected. Antituberculosis medication regimens were reviewed for potential medication errors, which were categorized as dosing errors, drug interactions, omission of therapy and inappropriate continuation of therapy in the presence of drug toxicity. Correct dosing of antituberculosis drugs was determined using ideal body weight in accordance with the 2003 national guidelines for the treatment of tuberculosis.[8] Contraindicated drug–drug interactions in patients co-infected with tuberculosis and HIV were identified based on the guidelines for both tuberculosis and use of antiretroviral agents in HIV-infected patients.[8,9] Of note, due to changes in dosing recommendations from treatment guidelines at the time of the study, rifabutin dosing of 150 mg three times a week, 300 mg three times a week or 150 mg once daily was considered acceptable when prescribed in HIV-infected patients receiving a ritonavir-boosted protease inhibitor. Hepatotoxicity was defined in this study as alanine transaminase and/or aspartate transaminase values greater than five times the upper limit of normal. Analysis of the data was conducted using descriptive methods. The study protocol was approved by the institution's Institutional Review Board.

RESULTS

Seventy-two patients receiving antituberculosis therapy for suspected or confirmed active tuberculosis disease were identified during the study period (Table 1). Approximately half of all patients were men, and most were of African American or Hispanic descent. The mean patient age was 41·9 years (range 0–84 years). Twenty-four patients had HIV infection with 19 patients receiving concomitant antiretroviral therapy. Infectious diseases consultation was provided in 44 patients, 54 patients received pulmonary consultation, 31 patients received consultations from both services, and five patients were not seen by either specialty. Antituberculosis therapy was initiated for the following indications: suspected tuberculosis disease based on clinical presentation and at least one positive acid-fast bacilli stain (32/72, 44%), suspected disease based on clinical presentation and radiographic findings (9/72, 13%), suspected disease based on clinical presentation and positive interferon-gamma release assay indicating prior exposure (4/72, 6%), prior diagnosis of tuberculosis disease with suspected recurrence (10/72, 14%), and empiric therapy without microbiological evidence of tuberculosis (17/72, 24%). Sixty patients received a 4-drug treatment regimen predominantly consisting of rifampin (or rifabutin), isoniazid, pyrazinamide and ethambutol (RIPE regimen). A 3-drug regimen was prescribed in ten patients and inadequate regimens with only two antituberculosis agents were used in two patients. Second-line agents, such as fluoroquinolones and aminoglycosides, were prescribed in five patients in place of a medication typically included in the standard RIPE regimen.

More than half of all patients experienced at least one medication error associated with antituberculosis therapy (44/72, 61%) with an overall average of 0·9 errors per patient (1·5 errors per patient among subgroup with errors). Of the total number of medication errors, most (56/66, 85%) remained uncorrected during the patient's hospital admission. Dosing errors were the most common type of medication error identified; three dosing errors were associated with rifampin, eight errors with isoniazid, 30 errors with pyrazinamide, and 16 errors with ethambutol (Fig. 1). Discrepancies between ethambutol and pyrazinamide

Table 1. Patient characteristics and management results

Characteristic	Result [*n* (%) unless otherwise specified]
Number of patients	72
Age, mean years (range)	41·9 (0–84)
Gender	
Male	37 (51·4)
Female	35 (48·6)
Race/ethnicity	
African American	30 (41·7)
White/Hispanic	24 (33·3)
White/non-Hispanic	4 (5·6)
Other/unknown	14 (19·4)
Number of patients with HIV infection	24 (33·3)
Receiving antiretroviral therapy	19 (26·4)
Number of antituberculosis drugs prescribed per regimen	
2 drugs	2 (2·8)
3 drugs	10 (13·9)
4 drugs	60 (83·3)
Selection of antituberculosis drugs	
Rifampin	53 (73·6)
Rifabutin	18 (25)
Isoniazid	67 (93·1)
Pyrazinamide	66 (91·7)
Ethambutol	64 (88·9)
Receipt of consultation	
Infectious diseases	44 (61·1)
Pulmonary	54 (75)
Both	31 (43·1)
Neither	5 (6·9)

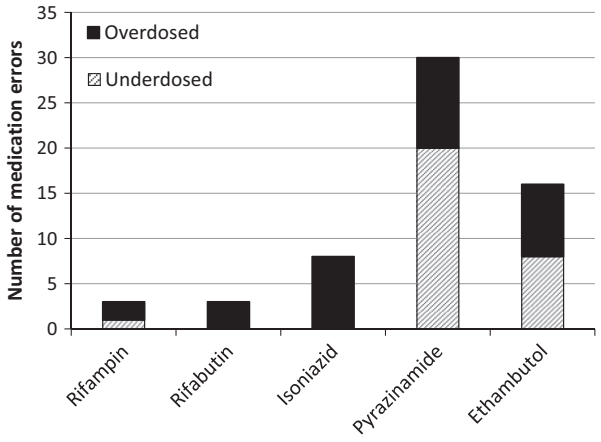

Fig. 1. Dosing medication errors by anti-tuberculosis agent.

dosing by guideline-defined weight ranges were observed in approximately one-third of patients receiving both medications (18/60, 30%). The large majority of these discrepant dosing errors were attributed to appropriate pyrazinamide dosing with overdosed or underdosed ethambutol based on the same weight range used for dosing the former agent. Of the four patients with renal impairment (defined as creatinine clearance less than 30 mL/min), doses of pyrazinamide and ethambutol were not adjusted for reduced renal function in three patients. Seven dosing errors related to drug interactions with antiretroviral therapy were identified, particularly due to concomitant use of rifamycins and protease inhibitors.

The prevalence of antituberculosis medication errors identified in patients receiving consultation from infectious diseases, pulmonary, or both services were similar to the rate in those without consultation, with 64%, 58%, 63% and 60% of patients experiencing at least one medication error, respectively. Pyridoxine supplementation was not prescribed for the prevention of peripheral neuropathy in 12 of 67 patients receiving isoniazid (18%). Although pyridoxine is not recommended universally for all patients taking isoniazid, lack of pyridoxine supplementation was considered an error regardless of the presence or absence of risk factors for neuropathy in this study. Only seven patients developed hepatotoxicity following initiation of antituberculosis therapy. Among patients with elevated liver enzymes, two patients continued to receive rifamycin therapy when discontinuation of therapy was indicated.

DISCUSSION

Despite the availability of long-established and well-defined guidelines for the treatment of active tuberculosis disease, medication errors associated with antituberculosis therapy remain a common occurrence in clinical practice. Newark, NJ, has a high rate of tuberculosis cases compared with most other US cities, and healthcare practitioners in University Hospital have more clinical experience managing patients with this infection. Despite this, errors in prescribing, administering and monitoring antituberculosis medications were identified in more than half of all patients receiving a multidrug regimen for the treatment of suspected or confirmed active disease. Furthermore, the large majority of these errors remained uncorrected during hospitalization, potentially leading to perpetuation of these errors during continued outpatient treatment, suboptimal response to therapy, development of resistance, increased risk for adverse effects and possible transmission due to insufficient treatment.

Previous studies evaluating medication errors associated with antituberculosis therapy were conducted more than two decades ago using similar retrospective, cohort study designs (Table 2). In a study of 35 patients with active, multidrug-resistant, pulmonary tuberculosis being treated in 1989 through 1990, 28 patients experienced at least one error related to deviation from treatment guidelines with an average of almost four errors identified per patient. Although initiation of inappropriate primary regimens and lack of pyridoxine supplementation with isoniazid were common errors reported in both our study and the previous study, other common errors noted in the previous study included failure to identify drug resistance, failure to identify non-adherence and inappropriate management of failing regimens.[5]

Table 2. Summary of studies evaluating medication errors associated with antituberculosis therapy

Study	Study population	Medication error rate	Most common medication errors
Mahmoudi A *et al.*[5]	35 Patients with multidrug resistant pulmonary tuberculosis	28/35 Patients (80%)	• Addition of single agent to failing regimen • Baseline or acquired drug resistance not identified • Inadequate primary regimen prescribed • Noncompliance not identified and/or addressed • Pyridoxine supplementation not given with isoniazid
Rao SN *et al.*[6]	110 Patients with culture-positive pulmonary tuberculosis	17/110 Patients (15%)	• Antituberculosis drug(s) underdosed • Inappropriate combinations prescribed • Inadequate duration of therapy
Jen SP *et al.* (current study)	72 Patients with suspected or confirmed tuberculosis disease	44/72 Patients (61%)	• Inappropriate dosing of antituberculosis drug(s) by weight • Inappropriate dosing for renal insufficiency • Dosing of antituberculosis drug not adjusted for drug-drug interactions • Pyridoxine supplementation not given with isoniazid

Another two year study examined 110 patients with culture-positive, pulmonary tuberculosis treated between 1994 and 1995, and demonstrated an error rate of approximately 15%. Most errors were secondary to suboptimal dosing of antituberculosis agents and/or inadequate treatment durations. Interestingly, the study investigators noted that patients treated by private physicians had a significantly higher rate of medication errors compared with those treated by the city's tuberculosis clinic.[6] In our study, the large majority of patients received consultation from the infectious diseases and/or pulmonary service; similar medication error rates were noted between patients with and without consultation from practitioners with expertise in tuberculosis management. The notable difference in reported rates of error between our study and the other published studies may be attributed to the types of medication errors included in each study, varying proportions of patients with HIV infection (and receiving antiretroviral therapy), and changes in diagnostic and treatment practices over time. However, the prevalence of medication errors associated with antituberculosis therapy in our study is similar to the rate of medication errors identified with antiretroviral therapy in our institution.[10]

There are several limitations to our study and its application to clinical practice in other geographical locations. Our results were based on a retrospective review of a fairly small number of patients with suspected or confirmed active tuberculosis receiving antituberculosis therapy within a 3 year period. Medication errors were identified during the patients' hospital admissions, but evaluation of each patient's medication regimen following discharge was not conducted. While most admitted patients from University Hospital receive outpatient follow-up at the Global Tuberculosis Institute, changes in medication error rates over the treatment course were not assessed. Furthermore, patients' lengths of stay were not collected and the duration of time available to correct medication errors identified during hospitalization could not be determined. The impact of antituberculosis medication errors on treatment outcomes, adverse effects and drug resistance were outside the scope of this study. One-third of the patients included in our study were HIV-positive, and most were receiving antiretroviral therapy. Drug interactions associated with concomitant antituberculosis and antiretroviral therapy may be infrequent in other areas with a lower prevalence of HIV infection, although rifamycins are associated with significant drug interactions with several other classes of medications. Lastly and most importantly, our study likely underestimates the true rate of errors associated with antituberculosis therapy as we focused on medication errors rather than overall management errors. As the prevalence of tuberculosis decreases and clinician experience with the infection wanes, the potential for errors when managing patients with suspected or confirmed tuberculosis disease may become even higher than the rate observed in our study.

Several measures can be considered to minimize the occurrence of medication errors associated with antituberculosis therapy. Although the feasibility and effectiveness of these interventions have not been evaluated specifically for antituberculosis therapy, they are considered recommended measures to optimize overall antimicrobial use in stewardship programmes.[11] Provider education on appropriate treatment regimens, antituberculosis medication dosing, potential drug–drug interactions, monitoring parameters and duration of therapy must be reinforced to ensure appropriate care to patients with active tuberculosis. Implementation and optimization of healthcare technology systems can encourage appropriate drug selection and dosing, provide drug information references and identify potential errors at the time of order entry. Therapeutic drug monitoring for antituberculosis medications is available for patient use, but not routinely done; therefore, proper dosing when initiating therapy is essential. Routine review of antituberculosis regimens could also be incorporated into the routine responsibilities of designated providers (infectious diseases or pulmonary attending physicians, fellows, pharmacists, etc.) or an institution's antimicrobial stewardship activities.

WHAT IS NEW AND CONCLUSION

Medication errors associated with antituberculosis therapy remain a common occurrence in the current clinical practice setting. Our institution serves a community with a relatively high prevalence of tuberculosis and the majority of admitted patients on antituberculosis therapy receive consultation from a clinician specializing in this condition, yet medication errors were identified in more than half of all patients evaluated in this study. The prevalence of medication errors has not improved over the past two decades with the implementation and dissemination of well-established treatment guidelines. Strict vigilance and routine monitoring of patients receiving antituberculosis medications is necessary to identify medication errors and minimize their impact on treatment outcomes. Although tuberculosis cases are declining in the United States, elimination of tuberculosis remains elusive. The decline in cases, without a heightened focus on at-risk communities, may lead to a further dearth of expertise and awareness of tuberculosis as public funds and attention are diverted. Progress towards tuberculosis elimination requires a multidisciplinary approach including detailed treatment management and monitoring of people with tuberculosis disease.

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CONFLICT OF INTEREST

None.

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