P1068: Quantifying Antimycobacterial Treatment-Related Harms Among Patients with Non-Tuberculosis Mycobacterium Infections: An Opportunity for Novel Agents?

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Introduction

Due to the chronic nature of non-tuberculosis mycobacteria (NTM) infections, long-term therapy with multidrug regimens is required to achieve clinical cure. Many of these agents are associated with profound toxicity profiles. Limited data is available to adequately describe and compare NTM regimens. The purpose of this study was to quantify the incidence of and determine predictors for adverse events associated (ADE) with NTM antimycobacterials.

Methods

Study Design and Objectives

This was an IRB approved, single center retrospective cohort study conducted at the Henry Ford Health System located in southeast Michigan, USA. The study objective was to quantify the incidence of and risk factors for antimycobacterial-associated adverse drug events (ADE) in NTM patients who receive outpatient therapy.

Subjects

The study population included patients diagnosed with NTM infections who received long-term anti-mycobacterial treatment between 2013 to 2022 and who met the following criteria:

Inclusion Criteria	Exclusion Criteria
• ≥18 years of age • Microbiologically confirmed NTM infection • ≥1 documented follow-up outpatient visit within 3-months of index NTM-encounter	• *Mycobacterium avium* complex (MAC) • ≤1 month of antimycobacterial treatment

Data Collection and Endpoints

Data were collected from the electronic medical record using a standardized electronic case report (REDCap).

Primary Composite Endpoint, from treatment initiation up to 12 months

i. **Acute kidney injury** was defined using the Acute Kidney Injury Network (AKIN) criteria.

ii. ***Clostridioides difficile* infection** included any positive *C. difficile* stool test accompanied by ≥3 unformed stools in a 24-hour period where other causes of diarrhea were excluded.

iii. **Thrombocytopenia** was defined three ways: 1) platelets < 50,000 (threshold used to consider interventions such as withholding anticoagulants), 2) platelets < 20,000 (threshold used to consider blood transfusion) and 3) platelet decline of ≥ 50%.

Secondary endpoints included any ADE/intolerance resulting in antimycobacterial regimen modification as noted by the prescriber in the electronic medical record.

Analysis

Descriptive measures were used to describe the patient populations and infection characteristics. To assess the incidence and predictors for adverse events associated with NTM therapy, bivariate analyses were performed. Categorical data was compared using Chi-square tests, continuous data was compared with the Mann-Whitney U test. *P*-values of <0.05 were considered significant. Statistical analysis was completed with SPSS Software for MacIntosh v. 29.0.

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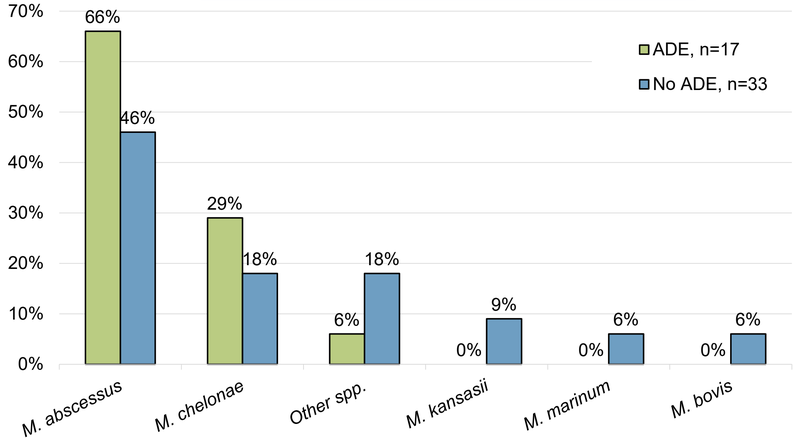
Results

Baseline Patient & Infection Characteristics

- A total of 50 patients were included: 17 (34%) developed ADE, 33 (66%) did not develop ADE.

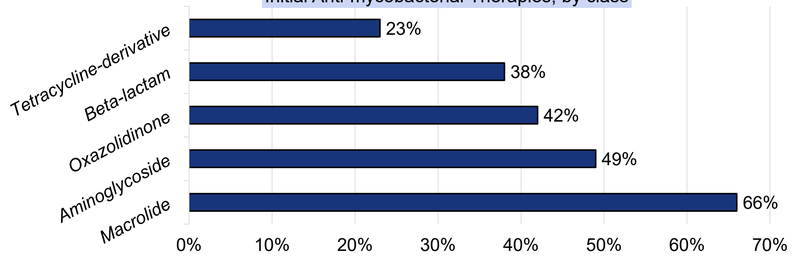
Characteristic *n* (%) or median (IQR)	Antimycobacterial ADE *n*=17	No ADE *n*=33	*P*-value
Patient Characteristics			
Age, years	66 (58-74)	64 (57-72)	0.89
Male sex	9 (52%)	20 (61%)	0.60
White/Caucasian race	4 (24%)	12 (36%)	0.36
Comorbid Conditions			
Tobacco use	3 (18%)	4 (12%)	0.68
Auto-immune disease	5 (29%)	4 (12%)	0.24
Gastroesophageal reflux disease	6 (35%)	8 (24%)	0.50
Chronic obstructive pulmonary disease	6 (35%)	9 (27%)	0.56
Interstitial lung disease	1 (6%)	4 (12%)	0.65
Ventricular assist device	0	3 (10%)	0.54
Infection Characteristics			
Index NTM infection	14 (82%)	30 (90%)	0.40
NTM disease type, non-inclusive			
Nodular	8 (47%)	10 (31%)	0.28
Fibro-cavitary	1 (6%)	1 (3%)	1.0
Other pulmonary	4 (24%)	12 (38%)	0.32
Non-pulmonary	8 (47%)	13 (41%)	0.67

Non-tuberculosis Mycobacteria Organism Distribution, *n*=50



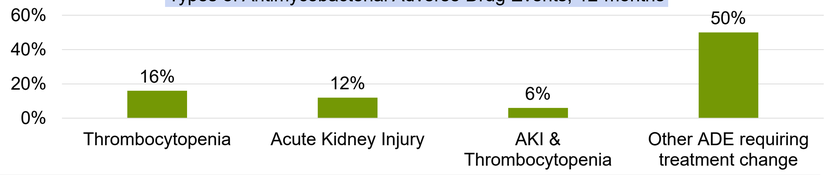
Antimycobacterial Treatment & ADEs

Initial Anti-mycobacterial Therapies, by class



- No patient received initial therapy with all oral agents.

Types of Antimycobacterial Adverse Drug Events, 12-months



- No patients developed *C. difficile* infection. The most common other ADE requiring treatment change were gastro-intestinal side effects, catheter-related infection, decrease in platelets that did not meet primary composite endpoint definition, and hearing loss.
- The median (IQR) time to ADE was 34 (23-64) days. Any other ADE/intolerance resulting in therapy modification occurred in 25 (50%) patients; the median (IQR) time to event was 36 (23-63) days.

Factors Associated with Antimycobacterial-associated ADE

Characteristic (*n*, %)	UnAdjOR (95%CI)	*P*-value
Aminoglycoside-based regimen	10.9 (2.5-47.4)	<0.001
Oxazolidinone-based regimen	5.6 (1.5-20.6)	0.007
Prior antibiotic exposure, 90-days	3.8 (0.96-15.2)	0.78
M. abscessus infection	2.2 (0.66-7.4)	0.19
Solid organ transplant recipient	4.2 (0.61-28.9)	0.15

Summary

- Antimycobacterial-associated ADE in NTM-infected patients are common and occur near the first month of treatment initiation. Subsequent treatment modifications due to ADEs are very common.
- Regimens that contained aminoglycosides or oxazolidinones had an association with an ADE.
- Intensified anti-mycobacterial monitoring may be an appropriate approach to avoid patient harm and represents an opportunity for outpatient antimicrobial stewardship programs.