with surgical debridement, and functional loss. Herein we describe our experience with such infections.

Methods. Records for adult patients from two academic, tertiary facilities with culture-proven NTMI involving the upper extremity were retrospectively reviewed. Demographic information, co-morbidities, laboratory and microbiological evaluation, management, and outcomes were extracted. Patients were analyzed based on pathogen identified and immune suppression.

Results. 77 patients were identified. The mean age was 59 years and 65% of patients were male. 48% reported a preceding injury, with the hand being most frequently involved (58%). 41% were considered immune compromised; 19% of them were organ transplant recipients. Mean symptom duration prior to presentation was 203 days. Mean time to culture identification was 33 days, and 25 different species of NTM were identified (subcategorized as rapid or slow growers). 77% had solitary lesions, with cutaneous/subcutaneous location as the most common site. All patients underwent surgical debridement with four undergoing amputation to control infection. 69% received combination antimicrobial therapy for a mean duration of 184 days. Immunosuppressed patients were treated with antimicrobial therapy for a longer duration (mean 243 vs 155 days). One-third of patients experienced complications and/or recurrence regardless of organism type.

Conclusion. NTMI of the upper extremity is often misdiagnosed leading to significant delays in appropriate management. Knowledge of its protean manifestations and early consideration in the differential diagnosis of chronic, painful swelling of the hand or wrist, nodular or inflammatory lesions, or septic arthritis is crucial. A low threshold for surgical or biopsy with specimens sent for histopathology as well as microbiologic analysis is warranted. A combined approach with surgical debridement and prolonged combination antimicrobial therapy is necessary for optimal outcomes; however, adverse reactions from such therapy are commonly encountered.

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1390. Durlobactam, a Diazabicyclooctane (DBO) β-lactamase Inhibitor (BLI), Inhibits BlaC and Peptidoglycan (PG) Transpeptidases of *Mycobacterium tuberculosis (Mtb)*: A Novel Approach to Therapeutics for Tuberculosis (TB)?

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Background. Novel therapies for multidrug-resistant TB are needed and new BLIs could answer this call. *Mtb* encodes for BlaC, a class A β-lactamase. BlaC is inhibited by clavulanate (CLA) while the DBO avibactam (AVI) is an inefficient inhibitor (low k_2/K value). Carbapenems are hydrolyzed slowly by BlaC (low *k*cat/*K*m value) making them "dual action" compounds that inhibit both BlaC and PG transpeptidases, the intended β-lactam targets. DBOs inhibit PG transpeptidases in other bacteria. To explore the therapeutic potential of new DBOs against *Mtb*, we compared the inhibition activity of AVI, relebactam (REL), and durlobactam (DUR, formerly ETX2514) against BlaC and *Mtb* PG transpeptidases using a biochemical approach. We also investigated the ability of DUR to lower minimum inhibitory concentrations (MICs) of β-lactams against *Mtb* H37Rv.

Methods. Mass spectrometry was performed to capture acyl-enzyme complexes (AECs) of purified BlaC and PG transpeptidases (PonA1, Ldt_{Mt1}, Ldt_{Mt2}, Ldt_{Mt3}, and Ldt_{Mt5}) with β-lactams and BLIs. Steady-state enzyme kinetics were determined using nitrocefin as a substrate. MICs with amoxicillin (AMX), meropenem (MER), CLA, and DUR alone and in combination against *Mtb* H37Rv were assessed using a microdilution method.

Results. DUR alone had a MIC of 2 µg/mL with *Mtb* H37Rv (Table 1). BlaC formed AECs with all carbapenems and BLIs. BlaC had lower Ki_{app} and higher $k2/K$ with DUR than those with AVI and REL and comparable to those with CLA; however, with a period of pre-incubation, AVI fully inhibits BlaC (Table 2). The carbapenems and DUR formed the most AECs with PG transpeptidases of the β-lactams and BLIs respectively; PG transpeptidases had lower Ki_{app} values with DUR than those with AVI (Table 3).

Table 1. Minimum Inhibitory Concetrations for Mycobacterium tuberculosis H37Rv

Antibiotic	MIC (µg/mL)
	H37Rv
Amoxicillin	32
Meropenem	32
Clavulanate	32
Durlobactam	2
Amoxicillin + 2.5 µg/mL Clavulanate	2
Amoxicillin + 4 µg/mL Durlobactam	0.5
Meropenem + 2.5 µg/mL Clavulanate	2
Meropenem + 4 µg/mL Durlobactam	≤ 0.125

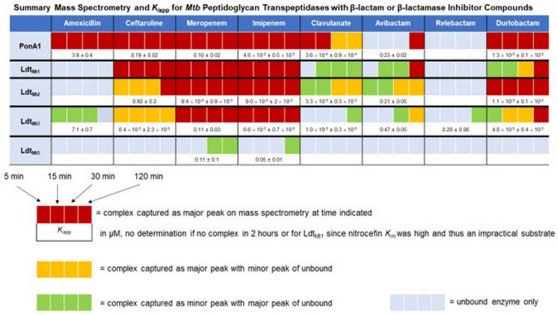
Kinetic parameters of BlaC inhibition with β-lactamase inhibitors and nitrocefin as a substrate

	$K_{i\,app}$ (µM)	k_2/K ($M^{-1}s^{-1}$)	k_{off} (s^{-1})	$t_{1/2}$ (min)	K_d (nM)	k_{cat}/k_{inact}
Clavulanate	3.3 ± 0.6	8400 ± 840	$4.0 \times 10^{-4} \pm 0.4 \times 10^{-4}$	29 ± 3	48 ± 5	8
Avibactam	>250	48 ± 8	*	ND	ND	2
Relebactam	>250	25 ± 11	**	ND	ND	10
Durlobactam	9.2 ± 0.9	5600 ± 560	$4.0 \times 10^{-4} \pm 0.4 \times 10^{-4}$	29 ± 3	71 ± 7	1

$K_{i\,app}$, apparent Michaelis constant of the inhibitor
k_2/K, "on" rate constant
k_{off}, off-rate constant
$t_{1/2}$, half life
K_d, dissociation constant
k_{cat}/k_{inact}, turnover number with 24-hour incubation of BlaC and inhibitor
* Unable to determine as avibactam inhibited activity after pre-incubation with 1.25 mM
**Unable to determine as relebactam did not inhibit even after pre-incubation 1.25 mM
ND, not determined with no k_{off} determined

$$E + I \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} E{:}I \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} EI$$

Summary Mass Spectrometry and K_{app} for *Mtb* Peptidoglycan Transpeptidases with β-lactam or β-lactamase Inhibitor Compounds



Conclusion. DUR alone has some antimicrobial activity against *Mtb* H37Rv. The likely mechanism that underlies this activity is inhibition of BlaC and several PG transpeptidases. Inhibition of enzyme targets with DUR was more potent and efficient than AVI and REL. DUR in combination with β-lactams lowered MICs but the DUR concentration used was higher than its MIC. Our findings support the exploration of novel BLIs against BlaC and PG transpeptidases with the ultimate goal of repurposing these drugs for the treatment of TB.

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1391. Body Mass Index and Leptin Levels at Different Stages of the Tuberculosis Spectrum

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Session: P-80. Tuberculosis and other Mycobacterial Infections

Background. Leptin is an adipose tissue-derived cytokine that plays a role in energy regulation and immune functions. High leptin levels and obesity have been associated with decreased risk of developing active TB. We aimed to characterize the association between body mass index (BMI) and leptin levels in patients at different stages of tuberculosis (TB).

Methods. Data from a cross-sectional cardiovascular risk study of 40 to 70 years old individuals enrolled in Lima, Peru, and Cincinnati, US, were analyzed. Four categories based on TB and treatment status were defined: no TB infection (QuantiFERON-TB test negative; n= 31), latent TB infection (LTBI; QuantiFERON-TB test positive; n= 43), active TB on treatment (in the continuation TB treatment phase; n= 30), and post-TB (within one year of TB treatment completion; n=16). BMI and plasma leptin levels were compared among the four groups using the Kruskal-Wallis test, followed by Dunn's multiple comparison test if differences were found in the Kruskal-Wallis test. Multivariate ordered logistic regression models were used to assess factors associated with leptin levels, adjusted for potential confounders.

Results. The median age was 53 years, and 51% were female. BMI was different between study groups (p< 0.01), with LTBI individuals having the highest BMI compared to other groups; see Figure 1A. Leptin levels were marginally low in the group with active TB on treatment, but no significant differences were found between groups (p=0.44; see Figure 1B). In multivariate analysis, leptin was associated with female sex (OR 23, 95%CI, 9-58), BMI (OR, 1.5, 95%CI, 1.2-1.7), and coronary plaque ≥25% stenosis (OR, 0.29, 95%CI, 0.08-0.99). Body mass index (BMI) and plasma leptin levels in participants with negative QuantiFERON-TB test (QFN-), latent tuberculosis infection (LTBI), active tuberculosis on treatment (ATBT), and post-TB treatment (TB-treated).