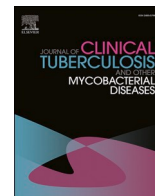


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Linezolid use for the treatment of multidrug-resistant tuberculosis, TB centers of excellence, United States, 2013–2018

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ABSTRACT

Background: In 2019, the World Health Organization released guidelines reflecting major changes in multidrug-resistant tuberculosis (MDR-TB) management—prioritizing fluoroquinolones, bedaquiline, and linezolid (LZD) while de-emphasizing previously favored injectable agents. In some cases, linezolid use is associated with gastrointestinal intolerance, mitochondrial toxicity, and significant drug interactions. CDC's Division of Tuberculosis Elimination supports a network of regional TB Centers of Excellence, which provide medical consultation to healthcare providers. Consultations are documented in a medical consultation database (MCD) enabling evaluation of management questions and recommendations. We describe the scope of clinical inquiries and responses specific to linezolid use for MDR-TB in the US.

Research Question: What are the major themes of provider and patient challenges regarding the use of linezolid for the treatment of MDR-TB in the US?

Methods: We queried MCD consults categorized as “MDR/XDR-TB” from 1/1/2013 to 12/31/2018. Only linezolid-specific consultations were included; incomplete and duplicate entries were excluded as were those citing linezolid historically or theoretically. Subgroup characteristics were assessed (e.g., Center, year, provider type). A descriptive coding scheme was developed through inductive thematic analysis.

Results: In 2013–2018 of the 1889 consults regarding MDR/XDR-TB, 934 MDR-TB consults referenced linezolid; 137 met inclusion criteria, representing between 4 and 10% of MDR-TB consults annually. Four main themes emerged: adverse effects (71.5%); concerns about linezolid use due to co-morbidities or concurrent medication use (15.3%); dosing adjustments (8.8%); and monitoring and maintenance logistics (4.4%).

Interpretations: Linezolid consults consistently exceeded 4% of all consults annually over the 6-year period, suggesting a need for access to expert opinion for providers using linezolid to manage MDR-TB. While only a snapshot of MDR-TB in the US, this evaluation summarizes major provider concerns regarding particular adverse effects, and highlights a need for evidence-based guidance regarding linezolid dosing and toxicity management.

Abbreviations: CITC, Curry International Tuberculosis Center; COE, Center of Excellence; GTBI, Global Tuberculosis Institute; HNTC, Heartland National Tuberculosis Center; LZD, Linezolid; MCCT, Mayo Clinic Center for Tuberculosis; MCD, Medical Consultation Database; MDR-TB, Multidrug-Resistant Tuberculosis, a form of infection caused by the bacterium *M. tuberculosis* that is resistant to both isoniazid and rifampin; SSNTC, Southeastern National Tuberculosis Center; SSRI, Selective serotonin reuptake inhibitor; TB, Tuberculosis; TDM, Therapeutic drug monitoring; XDR-TB, Extensively Drug-Resistant Tuberculosis, a form of infection caused by the bacterium *M. tuberculosis* that is resistant to isoniazid and rifampin plus a fluoroquinolone and at least 1 of the following injectable medications: amikacin, kanamycin, or capreomycin.

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1. Background

In 2018, the World Health Organization released guidelines reflecting major changes in multidrug-resistant tuberculosis (MDR-TB) management. [1] In 2019, The American Thoracic Society, Centers for Disease Control and Prevention, Infectious Diseases Society of America, and European Respiratory Society released similar guidelines. [2] These new guidelines prioritize use of fluoroquinolones, bedaquiline, and linezolid while de-emphasizing the use of previously favored injectable agents, thus attributing preference to all-oral regimens, which have been associated with greater treatment tolerability and fewer adverse effects. [1] Data collected on 135 TB patients from California, New York City, and Texas undergoing MDR-TB treatment from 2005 to 2007 showed that 9% of patients died on therapy, and that severe adverse effects—depression or psychosis, hepatitis, hearing impairment, and renal impairment—each occurred in > 10% of patients. [3–4] Of these 135, 97% had sputum culture conversion, and 78% completed treatment. [4] In contrast, global MDR TB treatment success rates, defined as the sum of cure and treatment-completion rates, are reported as only 55%. [5] While treatment success is a primary universal objective, reducing drug toxicities associated with MDR-TB regimens is an increasing priority.

Convincing data exist regarding the adverse effects and decreased efficacy of injectable agents. [6] However, data concerning the tolerability and effectiveness of newly emphasized oral medications in the treatment of MDR TB are only now beginning to emerge. [6] Per a recent meta-analysis, MDR TB regimens using injectables, particularly kanamycin and capreomycin, have significantly lower treatment success rates compared with injectable-free regimens. [7] Linezolid was shown to have a significant favorable influence on treatment outcomes improving treatment success rates and reducing patient mortality. [7] Nonetheless, linezolid can be associated with gastrointestinal intolerance, mitochondrial toxicity (resulting in lactic acidosis, myelosuppression, and peripheral neuropathy), and significant drug interactions including serotonin syndrome potentiated when used concurrently with other serotonergic agents. [8–10] While recent data demonstrate the effectiveness of regimens using linezolid, concerns remain regarding prolonged linezolid drug exposure and adverse effects. [11]

To date, data on incidence of adverse effects secondary to medications used to treat MDR-TB collected in US surveillance systems have not been systematically analyzed. CDC's Division of Tuberculosis Elimination (DTBE) supports a network of national TB Centers of Excellence (COEs) that provide expert medical consultation for providers managing TB infection and disease. [12] Since 2008, the COEs have been capturing consultation information in a web-based, de-identified medical consultation database (MCD). Access to the MCD allows for evaluation of national concerns relating to MDR-TB management including medication-specific adverse effects. From 2013 to 2017, the CDC-funded COEs included Curry International TB Center (CITC), The Mayo Clinic Center for Tuberculosis (MCCT), The Global TB Institute (GTBI), Heartland National TB Center (HNTC), and Southeastern National TB Center (SNTC); in 2018, MCCT ceased to be a CDC-funded COE, and the number of COEs participating in the MCD was reduced to four.

From 2013 through 2017, the most reported consultation topics included TB medication pharmacology, diagnostic and laboratory queries, case management logistics, and questions concerning MDR/XDR-TB. [13] Consultations relating to MDR-TB were found to fall into four main thematic categories: initial management, complications and longitudinal treatment, contact management, and treatment completion. [14] Given the increasing importance of linezolid as a component of MDR-TB management, it is necessary to understand clinical challenges that physicians and patients may face during its use. Therefore, we conducted a review of the MCD to identify 1) major themes of linezolid-related consultations and 2) major themes of expert recommendations regarding linezolid use for patients with MDR-TB.

2. Methods

We queried the MCD for consultations by any of the 5 COEs marked 'MDR/XDR-TB' occurring from 1/1/2013 to 12/31/2018. A text search was done for the terms "linezolid," "LZD," "LNZ," and "Zyvox." Consultations that referenced at least one of these terms were evaluated for subgroup inclusion. Consultations were included if a specific question regarding the use, acquisition, or therapeutic role of linezolid was asked. Incomplete and non-MDR-TB-related consultations were excluded as were those referencing linezolid historically (e.g., as a previous part of the patient's MDR-TB regimen) or theoretically (e.g., as a potential future treatment consideration stipulating current regimen failure). Inadvertent duplicate entries of the same consultation were also excluded (Fig. 1).

We assessed consultation characteristics including Center consulted, call year, patient type (adult versus pediatric), caller setting (e.g., hospital, health department), and requesting provider type using Microsoft Excel. Demographic statistics were compiled for all consultations referencing "linezolid," "LZD," "LNZ," or "Zyvox" by text search and for consultations included in the study subgroup.

Thematic analysis was done for the subgroup using nVivo 12.0, a qualitative data analysis program [15]. Descriptive codes (i.e., codes which summarize the basic topic of discussion) were developed via an inductive approach (i.e., codes were developed as they emerged from the text rather than being pre-determined). Following coding completion, codes were aggregated into a codebook. To confirm replicability, all consultations were re-coded to ensure consistent coding categorization; all initial codes were maintained. A second team member then coded a random, 10-consultation sample to evaluate inter-coder reliability.

Consultations were coded as "follow-up" when the consultation text included the phrases "follow-up," "f/u," or "update;" referenced a prior conversation regarding the same patient; or provided a consultation identification number. All other consultations were considered "initial" consultations.

The consultation question was coded first; subthemes were not coded in a mutually exclusive manner. Related subthemes were aggregated into broader categories to develop major themes (e.g., a consultation referencing anemia and headache was coded only into the major theme of linezolid adverse effects, but the sub-themes of cytopenia and headache were both coded). Recommendations were not coded in a mutually exclusive manner and were aggregated into major themes (e.g., for recommendations citing needs both for a linezolid dose reduction and for vitamin B6 supplementation, both were coded). Results were assessed for the subgroup and for initial versus follow-up consultations to reduce potential coding inflation due to repeated follow-up consultations regarding the same patient.

The CDC determined this project was program evaluation and not human subjects research and, therefore, did not require IRB review.

3. Results

3.1. Quantitative analysis

Over 6 years, the COEs provided 1889 consults marked 'MDR/XDR-TB.' Of these, 934 referenced linezolid in their text, and 137 met inclusion criteria (Table 1, Fig. 1). Of the 137 consultations, 80 (58.4%) were requested by physicians and 131 (95.6%) concerned adult patients; most of the consultation requests came from health departments (55.5%, n = 76) and hospitals (21.9%, n = 30). The Center providing the most consults in this database was HNTC (54.0%, n = 74) followed by MCCT (21.9%, n = 30), then GTBI (11.7%, n = 16), SNTC (9.5%, n = 13), and CITC (2.2%, n = 3).

Annually, between 37 and 57% of all MDR/XDR-TB consults referenced linezolid, and, of these, between 4 and 10% met inclusion criteria (i.e., involved a therapeutic conversation about linezolid) (Fig. 2).

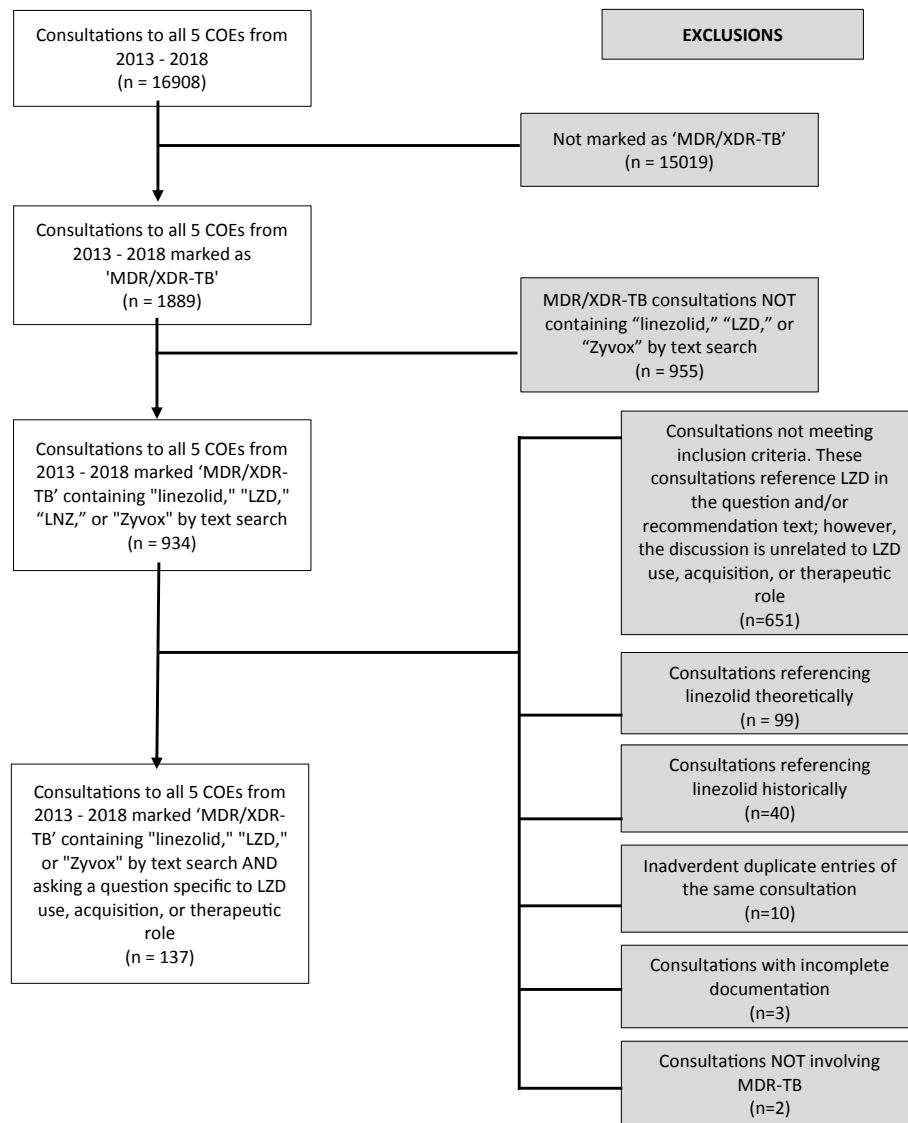


Fig. 1. Study inclusion and exclusion criteria. indicates excluded consultations.

3.2. Qualitative analysis

Of the 137 linezolid consultations included in our subgroup, 64 (46.7%) were coded as initial consultations and 73 (53.3%) as follow-ups. These consultations aggregated into four main themes (Table 2, Fig. 3): adverse effects, co-morbidities and concurrent medication use, dosing adjustments, and monitoring and maintenance logistics.

3.2.1. Linezolid adverse effect(s)

Most consultations (71.5%, $n = 98$) involved active adverse effect(s) known or suspected to be secondary to linezolid use (Table 3). The most commonly discussed subtopics were peripheral neuropathy ($n = 45$), cytopenias ($n = 41$), and visual disturbances ($n = 20$), of which 8 noted simultaneous use of linezolid and ethambutol.

The most noted cytopenias were isolated anemia ($n = 14$), isolated thrombocytopenia ($n = 8$), and concurrent anemia/thrombocytopenia ($n = 8$); however, leukopenia ($n = 5$), pancytopenia ($n = 3$), and concurrent leukopenia/thrombocytopenia ($n = 3$) were also described.

The five most common recommendations in response to consultations concerning adverse effect(s) were to perform additional evaluation (28.6%, $n = 28$), hold linezolid temporarily (28.6%, $n = 28$), continue linezolid (23.5%, $n = 23$), stop linezolid indefinitely with or without

initiating an alternative agent (18.4%, $n = 18$), and reduce linezolid dose (16.3%, $n = 16$) (Fig. 4). Recommendations were not mutually exclusive and multiple recommendations could possibly be attributed to a single consultation. Recommendations were categorized as “perform additional evaluation” if they referenced a need for further history or physical examination information ($n = 10$); specialist consultation ($n = 6$); or additional procedural, laboratory, or radiologic assessment ($n = 15$), of which 8 included a need for therapeutic drug monitoring (TDM). TDM was most often recommended for patients experiencing peripheral neuropathy symptoms ($n = 5$), followed by visual disturbances ($n = 2$) and cytopenias ($n = 1$). Inquiries about regimen adjustments following TDM results are referenced in the upcoming section “Linezolid Dosing Adjustments.”

Recommendations based on specific adverse effects are described in Fig. 5. For patients experiencing either peripheral neuropathy symptoms or visual disturbances, experts most often recommended additional evaluation; for patients with cytopenias, linezolid continuation was most commonly recommended. Additional evaluation was recommended 7 times for patients with visual disturbances—4 were recommendations to consult ophthalmology or optometry. Vitamin B6 supplementation was recommended 8 times by expert consultants; most were in response to a patient experiencing cytopenia(s) ($n = 5$).

Table 1
Consultations to Tuberculosis Centers of Excellence Referencing MDR/XDR-TB in the United States, 2013–2018, n = 1889.

Characteristic	Total MDR-TB (n = 1889)	Study cohort (n = 137)
Occupation of caller, n (%)		
Nursing	681 (36.1)	46 (33.6)
Physician	1051 (55.6)	80 (58.4)
Other*	150 (7.9)	11 (8.0)
Unknown	7 (0.4)	0 (0.0)
Type of consultation, n (%)		
Pediatric	269 (14.2)	6 (4.4)
Adult	1620 (85.8)	131 (95.6)
Setting of Caller, n (%)		
Academic Institution	64 (3.4)	9 (6.6)
Community Health Center	23 (1.2)	5 (3.6)
Corrections	40 (2.1)	5 (3.6)
Hospital	314 (16.6)	30 (21.9)
Local Health Department	657 (34.8)	32 (23.4)
Private Practice	47 (2.5)	7 (5.1)
Regional Health Office	85 (4.5)	1 (0.7)
State Health Department	555 (29.4)	44 (32.1)
Other	54 (2.9)	3 (2.2)
Refugee Clinic	42 (2.2)	1 (0.7)
Immigrant Clinic	7 (0.4)	0 (0.0)
Government clinic	1 (0.1)	0 (0.0)

NOTE: * Includes physician assistants, nurse practitioners, and all other staff under physician supervision

Bolded text indicates a category of consultation characteristic

For both peripheral neuropathy and visual disturbances, stopping linezolid, either temporarily (i.e., hold LZD) or permanently (i.e., stop LZD ± substitute another agent), was favored to continuing linezolid at either the current (i.e., continue LZD) or reduced dose. In contrast, experts more often recommended linezolid continuation for patients with cytopenias.

3.2.2. Co-Morbidities and concurrent medication use

A second major theme, accounting for 15.3% of consultations (n = 21), related to concerns about linezolid initiation or continuation in the setting of co-morbidities or concurrent medication use. The three most common subthemes included a history of adverse effects due to linezolid use (n = 9), a baseline hematologic abnormality or condition (n = 4),

and concurrent or proposed selective serotonin reuptake inhibitor (SSRI) use (n = 4).

Historical adverse effects due to linezolid use included a history of peripheral neuropathy (n = 2), lactic acidosis (n = 1), nausea and vomiting (n = 1), visual disturbance (n = 1), and hematologic disturbance (n = 3) comprising thrombocytopenia (n = 2) and leukopenia (n = 1). Baseline hematologic abnormalities or conditions included anemia (n = 1), thrombocytopenia (n = 1), concurrent leukopenia/thrombocytopenia (n = 1), and sickle cell disease (n = 1).

Most recommendations within this theme were to restart linezolid in patients who had previously used linezolid (n = 7) followed by the recommendation to start linezolid in linezolid-naïve patients (n = 4). Other recommendations included a 14-day SSRI washout before linezolid initiation (n = 2), hematology evaluation (n = 2), TDM to ensure appropriate drug levels (n = 2), restricted 6-month linezolid course (n = 1), and liquid to tablet formulation change (n = 1).

3.2.3. Linezolid dosing adjustments

A third theme encompassed linezolid dosing adjustments (8.8%, n = 12). Of these 12, six related to dose adjustments in response to linezolid drug level monitoring: 5 for sub-therapeutic levels and one for an elevated trough. Another 6 consultations were unrelated to drug-level monitoring and rather related to linezolid dose adjustment given a patient’s weight change (n = 1), improvement in a previously experienced adverse effect (n = 2), dosing frequency in relation to directly observed therapy (n = 1), or a dosing change proposed for an unspecified reason (n = 1).

Recommendations included a linezolid dose increase (n = 6), current linezolid dose maintenance (n = 4), and a linezolid dose reduction (n = 1).

3.2.4. Linezolid monitoring and maintenance logistics

A final theme concerned linezolid monitoring and maintenance logistics (4.4%, n = 6). These consultations involved inquiries about how and where to obtain drug level monitoring (n = 3), how and by whom visual monitoring should be done (n = 2), how to monitor and document neuropathy symptoms (n = 1), and whether there was a need for vitamin B6 supplementation with long-term linezolid use (n = 1).

Recommendations within this theme were more case-specific (e.g., in

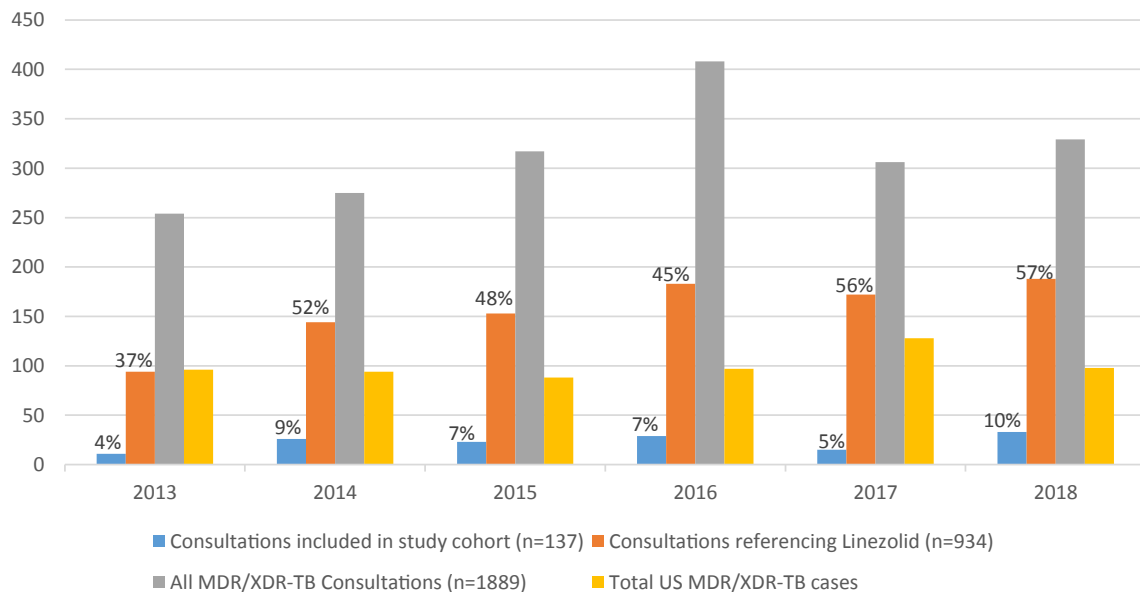


Fig. 2. Number of MDR-TB consultations to the Tuberculosis Centers of Excellence referencing linezolid or included in the study by year in the United States, 2013–2018, n = 1889. Bars indicate the absolute number of consultations included in the subgroup or referencing linezolid by text search by year. Percentages shown indicate the percent of all consultations marked MDR/XDR-TB for the given year that were included in the study cohort or referenced linezolid by text search. Note: Data for total U.S. MDR/XDR-TB cases from CDC Division of Tuberculosis Elimination, Reported Tuberculosis in the United States, 2018 [22].

Table 2
Themes of Consultations to Tuberculosis Centers of Excellence Referencing Linezolid in the United States, 2013–2018, n = 137.

Theme ^a	Study cohort, n (%)n = 137	Initial, n (%)n = 64	Follow-up, n (%)n = 73
Theme 1: Linezolid adverse effect (s) ^b	98 (71.5)	44 (68.8)	54 (74.0)
Theme 2: Co-morbidities and concurrent medication usage leading to concerns regarding linezolid initiation or continuation ^c	21 (15.3)	10 (15.6)	11 (15.1)
Theme 3: Linezolid dosing adjustments ^d	12 (8.8)	6 (9.4)	6 (8.2)
Theme 4: Logistics of linezolid monitoring and maintenance ^e	6 (4.4)	4 (6.3)	2 (2.7)

NOTE: ^a Theme categorization is mutually exclusive – cases are coded into only one of the four major themes.

NOTE: ^b Indicates the patient is currently experiencing adverse effect(s) including cytopenias, headache, lactic acidosis, nausea and vomiting, neuropathy, pancreatitis, and visual disturbances

NOTE: ^c Includes baseline hematologic abnormalities, pregnancy, history of linezolid adverse effect(s), and selective serotonin reuptake inhibitors. Excludes current adverse effect(s) relating to linezolid use.

NOTE: ^d Includes dose adjustments made given results of drug monitoring levels and those unrelated to drug level monitoring (e.g. following weight change or following an improvement in an adverse effect thought to be due to linezolid).

NOTE: ^e Includes need for Vitamin B6 supplementation, obtaining drug level monitoring, and administering visual assessments. Excludes dosing adjustments.

response to a question concerning drug level monitoring, checking linezolid levels at 2 and 6 h post-administration was recommended).

4. Discussion

This evaluation provides valuable information regarding US medical

provider use of linezolid, a now strongly recommended MDR TB medication. Our findings demonstrate the demand for expert consultation existing for many providers as evidenced by the increasing number of linezolid-specific consultations to the COEs over the 6-year period. The four identified major themes highlight common challenges providers face when managing MDR-TB with linezolid. [16–17] Most consultations referenced linezolid adverse effects, emphasizing the need for further education surrounding linezolid toxicity management and the value of expert consultation as a resource that enhances patient care and treatment outcomes.

Most adverse effects reported in this evaluation were attributable to mitochondrial toxicity: myelosuppression, lactic acidosis, and peripheral neuropathy. Song et al. showed a correlation between linezolid trough levels and mitochondrial toxicities—significantly lower toxicity rates were seen in patients with troughs < 2.0 µg/mL—supporting the proactive role of TDM with long-term linezolid use. [9] In our evaluation, most recommendations referencing TDM occurred in response to peripheral neuropathy symptoms with fewer TDM references for visual or hematologic disturbances. This may indicate a need for education regarding TDM as a means for monitoring and managing all mitochondrial toxicities. [18]

Many recommendations for managing adverse effect(s) included continuing linezolid at the current or reduced dose; continuation was recommended more often than discontinuing linezolid either permanently or temporarily. Recommendations to hold linezolid often included the potential for re-initiation. In response to co-morbidities and concurrent medication use leading to concerns about linezolid initiation or continuation, the most common recommendations were to restart linezolid or to begin linezolid in linezolid-naïve patients. These findings emphasize the importance and utility of linezolid within MDR TB regimens including improved culture conversion and cure rates, excellent tissue penetration and sterilizing effect, and the potential for injection-free administration. [19–20]

Optimal linezolid dose and duration are understudied topics of

Major Consult Themes

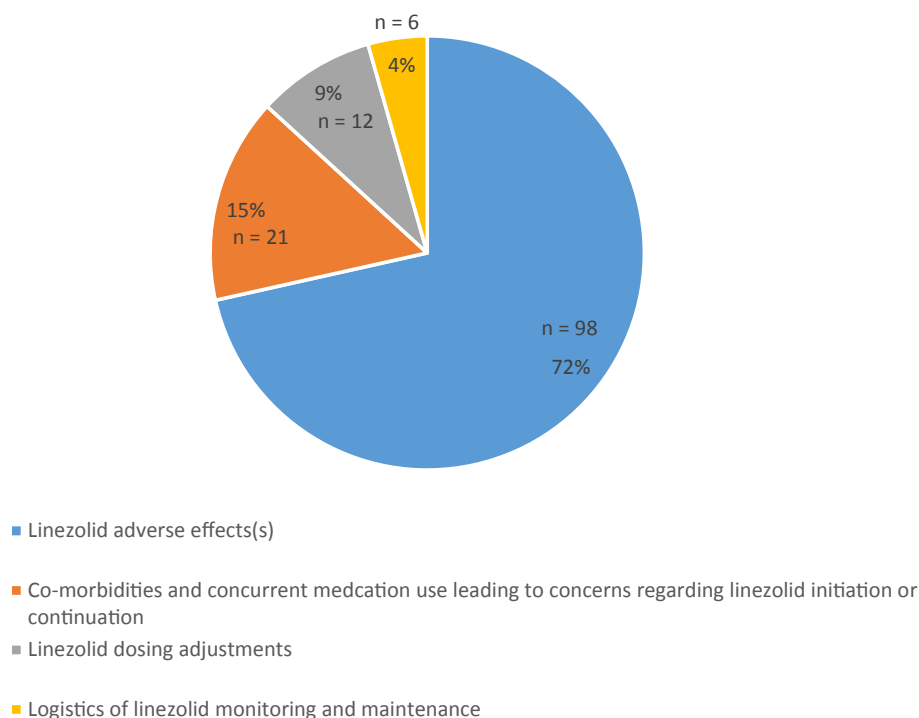


Fig. 3. Major themes of consultations to the Tuberculosis Centers of Excellence referencing linezolid in the United States, 2013–2018, n = 137.

Table 3

Themes, Sub-themes, and Codes of Consultations to Tuberculosis Centers of Excellence Referencing Linezolid in the United States, 2013–2018, n = 137. Percentages shown indicate the percent of consultations included in the study cohort that were further categorized into each subtheme.

Code ^a	Description	Study cohort, nn = 137	Initial, nn = 64	Follow-up, nn = 73
Theme 1: Linezolid adverse effect(s)				
Cytopenias	Patient experiencing a hematologic disturbance as an adverse effect to linezolid use	41 (29.9%)	16 (11.7%)	25 (18.2%)
Headache	Patient experiencing headache as an adverse effect to linezolid use	1 (0.7%)	1 (0.7%)	0 (0%)
Lactic Acidosis	Patient experiencing lactic acidosis as an adverse effect to linezolid use	2 (1.5%)	1 (0.7%)	1 (0.7%)
Nausea and Vomiting	Patient experiencing nausea and vomiting as an adverse effect to linezolid use	1 (0.7%)	1 (0.7%)	0 (0%)
Neuropathy ^b	Patient experiencing a peripheral neuropathy as an adverse effect to linezolid use	45 (32.8%)	20 (14.6%)	25 (18.2%)
Pancreatitis	Patient experiencing pancreatitis as an adverse effect to linezolid use	1 (0.7%)	1 (0.7%)	0 (0%)
Visual Disturbance ^c	Patient experiencing a visual disturbance as an adverse effect to linezolid use	20 (14.6%)	11 (8.0%)	9 (6.6%)
Theme 2: Co-morbidities and concurrent medication usage leading to concerns regarding linezolid initiation or continuation				
Baseline hematologic abnormality	Concern about initiation or continuation of linezolid due to a hematologic abnormality or condition (ex. Sickle Cell Disease) preceding linezolid use	4 (2.9%)	3 (2.2%)	1 (0.7%)
Current pregnancy	Concern about initiation or continuation of linezolid because the patient is currently pregnant	2 (1.5%)	0 ^d (0%)	2 (1.5%)
History of linezolid adverse effect	Concern about linezolid re-initiation due to a history of an adverse effect while using linezolid	9 (6.6%)	3 (2.2%)	6 (4.4%)
SSRI use	Concern about initiation or continuation of linezolid due to current or proposed use of a selective serotonin reuptake inhibitor (SSRI)	4 (2.9%)	3 (2.2%)	1 (0.7%)
Baseline neuropathy	Concern about initiation or continuation of linezolid due to the presence of pre-existing baseline	1 (0.7%)	1 (0.7%)	0 (0%)

Table 3 (continued)

Code ^a	Description	Study cohort, nn = 137	Initial, nn = 64	Follow-up, nn = 73
Patient is an infant	neuropathy in the patient. Concern about continuation of linezolid in a patient because the patient is an infant and unable to report symptoms or changes.	1 (0.7%)	0 ^d (0%)	1 (0.7%)
Current chemotherapy	Concern about initiation or continuation of linezolid due to current chemotherapy regimen.	1 (0.7%)	1 (0.7%)	0 (0%)
Theme 3: Linezolid dosing adjustments				
Dose adjustment related to linezolid drug level monitoring	Question regarding the patient's linezolid dose following the result of linezolid drug monitoring levels (e.g. trough level, serum level)	6 (4.4%)	5 (3.6%)	1 (0.7%)
Dose adjustment unrelated to drug level monitoring ^e	Question regarding linezolid dose adjustment unrelated to drug monitoring levels	6 (4.4%)	1 (0.7%)	5 (3.6%)
Theme 4: Logistics of linezolid monitoring and maintenance				
Logistics of drug level monitoring	Question regarding logistics of obtaining linezolid drug monitoring levels including trough and serum levels.	3 (2.2%)	1 ^d (0.7%)	2 (1.5%)
Logistics of administering assessments	Question regarding how and by whom to perform visual assessment in patients taking linezolid	2 (1.5%)	2 (1.5%)	0 (0%)
Need for B6 supplementation	Question regarding the need for vitamin B6 supplementation in long-term linezolid use	1 (0.7%)	0 ^d (0%)	1 (0.7%)
Logistics of monitoring and documenting neuropathy symptoms	Question regarding how to monitor and document for neuropathic symptoms in patients taking linezolid.	1 (0.7%)	1 (0.7%)	0 (0%)

NOTE: ^a Note: subthemes within each major theme were not exclusively coded. Cases within a single theme could be coded for multiple subthemes if applicable. Therefore, numbers within each column may not sum to the indicated n.

NOTE: ^b Excludes patients experiencing visual symptoms consistent with optic neuritis.

NOTE: ^c Includes consultations referencing a diagnosis of optic neuritis as well as signs and symptoms occurring without formal diagnosis such as visual blurring, changes in color vision, and decreased visual acuity.

NOTE: ^d The initial consult was not captured in the text search (i.e., did not mention "linezolid," "LZD," "LNZ," or "Zyvox") or inclusion criteria (i.e., did not involve a therapeutic conversation regarding linezolid use). However, the follow-up consultation was captured in the text search or met inclusion criteria.

NOTE: ^e Includes questions relating to dose adjustment following weight change or improvements in linezolid adverse effect(s) as well as questions relating to dose adjustment that do not indicate the reason for the proposed dose adjustment.

Bolded text indicates a major theme.

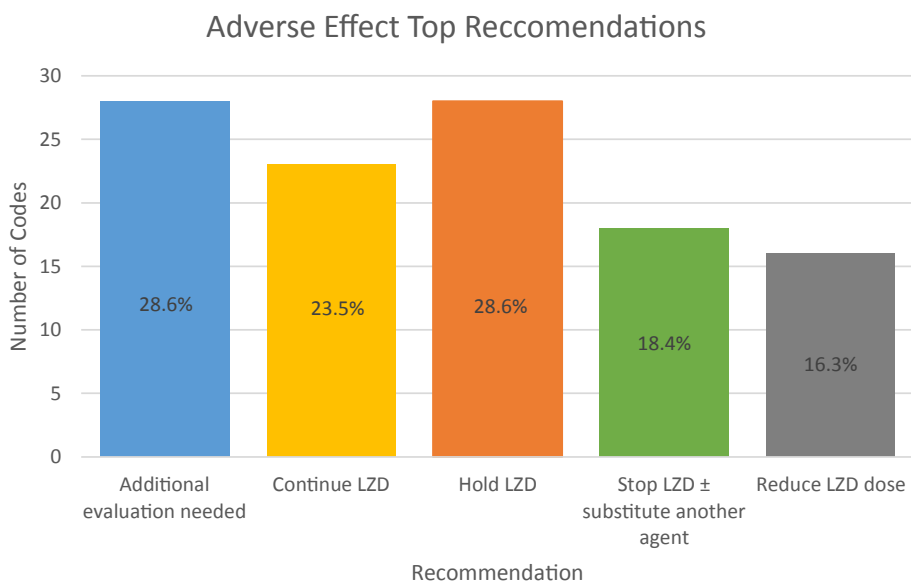


Fig. 4. Principal expert recommendations for consultations relating to linezolid adverse effects to the Tuberculosis Centers of Excellence in the United States, 2013–2018, n = 98. ^a Note that recommendations were not coded in a mutually exclusive fashion. Multiple recommendations could be coded for a single consultation if applicable. Additionally, 1 case did not include an expert recommendation and was not coded. Therefore, the totaled number of recommendations may not sum to the indicated n and the totaled percentages may not sum to 100%.

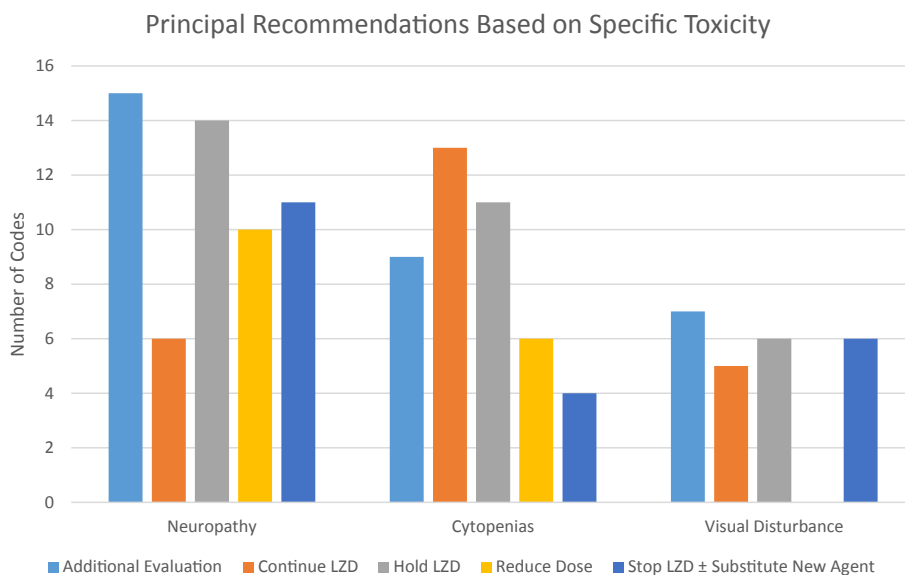


Fig. 5. Principal expert recommendations by specific toxicity for consultations relating to linezolid adverse effects to the Tuberculosis Centers of Excellence in the United States, 2013–2018, n = 98.

clinical interest. [17] Current studies, such as the LiMiT trial through the CDC-sponsored TB Trials Consortium, are underway evaluating dose-related linezolid safety, tolerability, and efficacy. [21] The COE consultation service was used for linezolid-dosing inquiries, but, notably, no consultations were requested regarding initial dosing. Instead, questions involved dose adjustments in the context of clinical or laboratory changes, indicating providers may be comfortable with initial management but seek consultation when the need for dose adjustment arises.

As with previous MCD evaluations, consultation requests most often came from health departments. [13–14] However, in this evaluation, 25% of consultations were requested from hospitals. Previous MCD reviews have shown that from 2013 through 2017 only 13% of all MCD consultations and 18% of all MDR-TB consultations came from hospitals. [13–14] The increased consultation service use by hospital-based providers suggests that the treatment of MDR-TB patients with linezolid is bipartite with short-term management, especially that of adverse effects,

assumed in a hospital setting and long-term care managed through health departments.

This study has several limitations. It only includes consultations made to TB COEs, which may not be representative of all national MDR-TB consultations. These consultations may include a disproportionate number of clinical challenges given the need for expert assistance. This contributes to a referral bias in the cases included in these consultations as challenging cases are likely more often referred to TB COEs for consultation than cases of linezolid use without toxicity or barriers. Additionally, as the cases included in this sample are limited only to these referrals and the true number of MDR-TB patients treated with linezolid in the TB COE jurisdictions examined is unknown, the rate of adverse events associated with linezolid use in this study is likely inflated. Because MCD information is de-identified, following cases longitudinally in this database is not possible unless a case identifier number were to be consistently given. Lack of longitudinal data limits our ability to evaluate outcomes using this database, and lack of

feedback from requesting providers hinders the evaluation of recommendation implementation and utility. While all providers use the same MCD template, variability exists in the style and detail of documentation as well as in the means of communication (i.e., phone versus email correspondence). Thus, we did not have the ability to account for missing or undocumented information that may have impacted the frequency or content of consultation topics. Despite these limitations, this evaluation identifies common provider concerns and corresponding expert recommendations regarding linezolid use for MDR-TB and may raise awareness about these challenges for providers in a multitude of settings.

5. Conclusion

As advances in MDR TB treatment are made following years of long, inadequate, and potentially toxic treatment courses, we must be aware of the complexity of current MDR TB management especially as new and re-purposed medications are more frequently used. Over a recent 6-year period, the TB COEs provided a considerable number of consultations regarding linezolid use in patients with MDR TB. While this is only a snapshot of MDR TB nationally, it summarizes major provider concerns, most of which have related to adverse effects, regarding linezolid use in this population. The findings presented here emphasize a demand for expert opinion and guidance regarding the use of newly recommended agents such as linezolid and highlight a need for additional clinical data concerning linezolid dosing and toxicity management.

Author contributions

AM contributed to project conception and performed data analysis and interpretation as well as drafting and revising this manuscript. MH, BS, JWW, AP, CH, ML, MD, and NDG contributed to project conception and critical revisions. All authors have given final approval for publication and agree to be accountable for this work.

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