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Combined Use of Meropenem, Linezolid, and Quinolones for Non-Drug-Resistant Tuberculosis in Critically Ill Patients and Other Settings: A Descriptive Series

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Uso combinado de meropenem, linezolid y quinolonas en el manejo de tuberculosis no asociada a resistencia a drogas antituberculosas en pacientes hospitalizados

ABSTRACT

Meropenem, linezolid, and quinolones are alternatives for managing tuberculosis (TB) in cases of drug-related adverse reactions, critical ill patients, organ failure, or inability to use the oral route. ***Aim:*** *To report the experience with the combined use of these compounds in cases of TB not associated with drug-resistant tuberculosis.* ***Methods:*** *Observational study of patients hospitalized for TB between 2020 and 2024 treated with these compounds at a regional hospital in Chile.* ***Results:*** *Ten male patients (median age 43.5 years), were treated with this combination either by adverse drug reactions (4 cases), hepatitis-liver failure (3 cases), respiratory failure, suspected gastrointestinal bleeding or a critical condition (1 each one). Combination therapy was used during the initial intensive (9 cases) or continuation phase (1 case). Median meropenem doses was 3 g/day for 2 weeks, 1,200 mg/day of linezolid for 2 weeks, and 750 mg/day of levofloxacin in 7 cases for 3 weeks or moxifloxacin (400 mg/day). Five patients were admitted to critical intensive care units. In 2 cases with a prolonged alternative treatment (≥ 4 weeks), M. tuberculosis culture became negative. Anemia secondary to linezolid was observed in 6 cases, one requiring transfusion. Linezolid and meropenem therapeutic drug monitoring was applied in one case. WHO treatment outcome was classified as treatment success in 4 cases, dead in 4 (3 treated on a premortem basis), abandonment in one, and one still under treatment.* ***Conclusions:*** *The combined use of meropenem, linezolid, and quinolones may be a viable option for managing hospitalized TB*

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patients with contraindications to standard oral treatment and may contribute to microbiological control and patient recovery. In some cases, it represents a desperate measure and may be associated with hematological adverse effects.
Keywords: *Linezolid; Meropenem; Quinolones; Tuberculosis.*

RESUMEN
Meropenem, linezolid y quinolonas son alternativas para el manejo de la tuberculosis (TB) en casos de reacciones adversas relacionadas con el fármaco, pacientes críticos, insuficiencia orgánica o imposibilidad de utilizar la vía oral. ***Objetivo:*** *Reportar la experiencia con el uso combinado de estos compuestos en casos de tuberculosis no asociada a tuberculosis farmacorresistente.* ***Método:*** *Estudio observacional de pacientes hospitalizados por TB entre 2020 y 2024 tratados con estos compuestos en un hospital regional en Chile.* ***Resultados****: Diez pacientes varones (mediana de edad 43,5 años), fueron tratados con esta combinación ya sea por reacciones adversas al fármaco (4 casos), hepatitis- fallo hepático (3 casos), insuficiencia respiratoria, sospecha de hemorragia gastrointestinal o paciente en estado crítico (1 cada uno). La terapia combinada se utilizó durante la fase inicial intensiva (9 casos) o de continuación (1 caso). La mediana de dosis de meropenem fue de 3 g/día durante 2 semanas, 1.200 mg/día de linezolid durante 2 semanas y 750 mg/día de levofloxacino en 7 casos durante 3 semanas o moxifloxacino (400 mg/día). Cinco pacientes ingresaron a unidades de cuidados intensivos. En 2 casos con un tratamiento alternativo prolongado (≥ 4 semanas), el cultivo de M. tuberculosis resultó negativo. Se observó anemia secundaria al linezolid en 6 casos, uno de los cuales requirió transfusión. En un caso se realizó monitorización de niveles plasmáticos de linezolid y meropenem. El resultado del tratamiento según criterios de OMS se clasificó como éxito del tratamiento en 4 casos, muerte en 4 (3 tratados en forma premortem), abandono en uno, y uno todavía en tratamiento.* ***Conclusiones:*** *El uso combinado de meropenem, linezolid y quinolonas puede ser una opción viable para el manejo de pacientes tuberculosos hospitalizados con contraindicaciones al tratamiento oral estándar y puede contribuir al control microbiológico y a la recuperación del paciente. En algunos casos, representa una medida desesperada y puede asociarse a efectos adversos hematológicos.*
Palabras clave: *Linezolid; Meropenem; Quinolonas; Tuberculosis.*

Meropenem, linezolid, and quinolones are alternatives for managing tuberculosis (TB) associated with drug-resistant strains[1,2]. They can also be used in cases of adverse drug reactions, critically ill patients, organ failure, or when oral administration is not feasible[3,4,5,6,7,8]. For example, in critically ill patients receiving enteral treatment, rifampin does not achieve adequate plasma concentrations in most cases (70%), and although less frequently, this also occurs with isoniazid and ethambutol[4,7]. Access to intravenous rifampin and isoniazid, which could overcome these pharmacokinetic limitations, is not widely available in Chile or is logistically complex, perpetuating therapeutic challenges. Additionally, severe adverse reactions to anti-TB drugs may prevent the use of rifampin or isoniazid even in the absence of drug resistance[5], while different organ dysfunctions, especially severe liver failure, further restrict the use of various anti-TB medications.

Local data indicate that a significant fraction of TB patients require hospitalization and face conditions like shock, digestive intolerance, adverse drug reactions, or surgical procedures that at least temporarily preclude oral TB treatment[5,9]. The inability to promptly initiate or maintain TB treatment is associated with higher morbidity, mortality, and impaired microbiological control of the disease. Consequently, in specific clinical scenarios, it becomes necessary to consider alternative combined regimens, even in the absence of resistance, to prevent adverse outcomes.

The purpose of this study is to share the experience with the combined use of these compounds in cases of TB not associated with drug resistance in hospitalized patients.

Patients and Methods

This is a retrospective observational study involving hospitalized patients with TB confirmed by culture, treated between 2020 and 2024 with meropenem, linezolid, and quinolones in a regional hospital in southern Chile. Treatment decisions were made jointly by the treating physicians and the local TB Control and Elimination Program (PROCET) representative. Cases were identified through investigator records, and clinical data of interest were extracted from medical records. Variables analyzed included TB presentation, reasons for using alternative treatment, treatment phase, administration route, doses, duration, and outcomes. Premortem use was defined as initiation ≤4 days before death. Results for quantitative variables are presented as non-parametric measures of central tendency and dispersion, and qualitative variables as percentages. The study was approved by the Scientific Ethics Committee of the Los Ríos Health Service.

Results

Ten male patients, with a median age of 43.5 years (IQR 39–55), were treated with this combination between 2020 and 2024. All cases were culture and/or PCR-confirmed; 9 had pulmonary involvement, and 6 had disseminated TB.

The reasons for combined use included adverse drug reactions in 4 cases (40%), such as rifampin-induced neutropenia or encephalopathy, isoniazid-induced gastroparesis with gastric retention, or hepatotoxicity (Table 1). In the remaining 6 cases, use was due to hepatitis or liver failure, respiratory failure, suspected gastrointestinal bleeding contraindicating oral administration for a few days, and a critical condition (Tables 1 to 3).

Combination therapy was used in the intensive initial phase (9 cases) or the continuation phase (1 case). Median doses were 3 g/day of meropenem (IQR 3-6 g/day) for 2 weeks (IQR 0.39-4.75 weeks), 1,200 mg/day of linezolid for 2 weeks (IQR 0.39-10.2 weeks), and 750 mg/day of levofloxacin in 7 cases for 3 weeks (IQR 0.42-20 weeks). Moxifloxacin (400 mg/day) was used intravenously in 2 cases for 0.1 and 2 weeks, and sequentially with levofloxacin in one case due to stock issues (Case 10, Table 2). Linezolid was administered intravenously in 6 cases or by sequentially oral or intravenous route in 4 patients. Five patients were treated in the ICU or intermediate care unit (50%). Amoxicillin-clavulanate was not used in any patient.

In one case, simultaneous monitoring of plasma levels of meropenem and linezolid was performed, showing a trough concentration for meropenem for 12.04 µg/mL and subtherapeutic

Table 1. General features and reason for use in 10 patients treated for tuberculosis with meropenem, linezolid, and quinolones, Hospital Valdivia, 2020-2024.

Variable	Result
Age in years median (IQR)*	43.5 (39-55)
Male gender n (%)	10 (100%)
Comorbid conditions	
Chronic lung disease, any n (%)	3 (30%)
Liver cirrhosis n (%)	2 (20%)
HIV/AIDS n (%)	1 (10%)
Immunosuppression due to anti-TNF-alpha n (%)	1 (10%)
Social risk factors	
Homeless n (%)	1 (10,0%)
Drug addiction or heavy alcohol consumption n (%)	3 (30%)
Migrant n (%)	2 (20%)
Malnutrition n (%)	9 (90%)
Weigh Kg median (IQR) in cases with data	49 (45-49)
Tuberculosis features	
Lung tuberculosis n (%)	9 (90%)
Disseminated tuberculosis n (%)	6 (60%)
Treatment abandonment n (%)	2 (20%)
Rifampicin resistance n (%)	0 (0%)
Reason for use	
Associated to adverse drug reaction n (%)	4 (40%)
Neutropenia by rifampicin	1
Bradipsiquia by rifampicin	1
Gastroparesis by isoniazid	1
Liver toxicity	1
Not Associated to adverse drug reaction n (%)	6 (60%)
Hepatitis or liver failure	3
Respiratory failure	2
Upper gastrointestinal bleeding suspicion	1
Critical ill	1
Treatment	
Meropenem weeks median (IQR)	2 (0.39-4.75)
Meropenem doses/day g median (IQR)	3 (3-6)
Linezolid weeks	2 (0.39-10.2)
Linezolid doses/day mg	1,200
Levofloxacin weeks	3 (0.42-20)
Lefofloxacin dose/day mg	750
Moxifloxacin weeks (2 cases)	0.1-2
Moxifloxacin doses/day mg	400
Amoxicillin-clavulanate	-

*IQR: interquartil range.

Table 2. Details of patients treated with meropenem, linezolid, and quinolones for non-drug resistance TB, Hospital Valdivia, Chile, 2020-2024.

Case	TB type, other details	Reason of use	Scheme, total duration, phase of treatment
1	Disseminated TB: lymph node, CNS, ocular, lung	CNS involvement and neutropenia secondary to rifampicin	Meropenem 4 weeks, linezolid 54 weeks, levofloxacin 54 weeks. Maintenance phase
2	Disseminated TB: Miliary, lung. Anti-TNF-alpha antibody receptor	Critically ill with shock, renal (serum creatinine 1.99 mg/dL), and respiratory failure (PaFiO2 85)	Meropenem 1.4 weeks. Linezolid and levofloxacin 0.6 weeks. Initial intensive phase
3	Lung TB	Hepatitis with increased serum AST* (5 times UPL**) and, ALT* (4 times UPL); associated diarrhoea	Meropenem + linezolid + moxifloxacin for 2 weeks. Initial intensive phase
4	Disseminated: Miliary, lung, spleen, lymph nodes AIDS without treatment	Liver failure with increased total bilirrubin (2.9 mg/dL), AST (7 times UNL) and ALT (2 times UNL), INR***also increased (1.46)	Meropenem + linezolid + levofloxacin for 3 weeks Initial intensive phase
5	Disseminated TB: Miliary, spleen, retroperitoneal, peritoneal Liver cirrhosis Child B stage	Liver failure: increased AST levels (2 times UNL), increased total serum bilirrubin (1.42 mg/dL) and INR 1.49	Meropenem + linezolid + moxifloxacin for 0.1 weeks Initial intensive phase. *Premortem* prescription
6	Disseminated TB: Miliary, Lung Liver cirrhosis Child A stage	Liver adverse drug reaction by anti-TB treatment during initial intensive phase: AST levels 22 times UNL, Total serum bilirrubin 8 mg/dL, INR 1.4.	Meropenem + linezolid for 2 weeks, levofloxacin for 12 weeks. Initial intensive phase
7	Lung TB	Upper gastrointestinal bleeding suspicion that impeded oral route	Meropenem + linezolid + levofloxacin for 0.4 weeks Initial intensive phase

...continuación tabla 2.

Case	TB type, other details	Reason of use	Scheme, total duration, phase of treatment
8	Lung TB. Drug addicted. 3 previous treatment abandonments	Gastroparesis secondary to isoniazid with vomiting	Meropenem + linezolid + levofloxacin for 23 weeks Initial intensive phase
9	Lung TB complicated with pneumothorax. Schizophrenia	Critically ill patient without oral available route	Meropenem + linezolid + levofloxacin for 0.3 weeks Initial intensive phase *Premortem* prescription
10	Lung TB complicated with pneumothorax. Treatment abandonment	Initially by respiratory failure (PaFiO2 129) with pleurostomy by pneumotorax. Later by encefalopathy secondary to rifampicin	Meropenem 7 weeks Linezolid 5.7 weeks Quinolones 6 weeks Initial intensive phase

*: AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ** UPL: upper normal limit; *** INR: international normalized ratio.

levels of linezolid (C_{min} 0.9 µg/mL; AUC24 35 mg*h/L) one week after rifampin discontinuation. Linezolid concentrations increased the following week to a C_{min} value of 6.75 µg/mL with an AUC24 of 126 mg*h/L (desired C_{min} value: 2-8 µg/mL and AUC24: 80-120 mg*h/L). This concentration was considered very close to the maximum desirable, prompting a reduction in the daily linezolid dose from 1200 mg to 600 mg. No further monitoring was conducted as linezolid was discontinued a few days later. This patient required a red blood cell transfusion prior to these measurements (Case 10, Figure 1).

Microbiological control: In three cases, the duration of the alternative treatment was ≥4 weeks, which was associated with negative cultures for *M. tuberculosis* cultures in two of them. In the remaining case, no follow-up sample was obtained during the period of alternative treatment.

Seven out of the ten patients were able to return to conventional oral treatment after the alternative therapy, although two of them died either in the hospital or after discharge. One patient in the series, who had disseminated TB and neutropenia caused by rifampin, received only the alternative treatment.

The combined treatment was associated with the parallel use of rifampin, ethambutol, isoniazid, or pyrazinamide for variable periods in three cases, administered in non-fixed doses regimens. According to WHO criteria, the discharge outcomes were treatment success in 4 (cured, 3; treatment completion, 1 case), treatment abandonment (1 case), and death (4 cases) (Table 3). The remaining patient, with a history of treatment abandonment, is still undergoing treatment (Case 10). In three of the four deceased cases, this treatment was initiated *premortem* (≤4 days before death).

The safety of these treatments was continuously analyzed exclusively from a hematological perspective. Among six cases with ≥1 week of linezolid use, a non-significant trend toward a decrease in hemoglobin levels was observed (median baseline value 10.6 g/dL, IQR: 9.8-12.5

g/dL; median lowest follow-up value 7.6 g/dL, IQR: 7.0-8.3 g/dL) (Figures 1 and 2). However, only one patient required a blood transfusion (Case 10, Figure 1).

Additionally, the neutrophil count curve was analyzed in patients who received ≥1 week of meropenem (n= 8), and no cases of neutropenia were observed (data not shown). Only one patient with hepatic cirrhosis but without baseline thrombocytopenia experienced a mild decline in platelet count by the end of the second week (from 315,000 to 109,000/mm^3), which reversed in the week following treatment discontinuation of linezolid.

The 10 cases described in this report represent 14.9% of the total number of patients hospitalized for TB between 2020 and October 2024 (67 cases).

Under the Transparency Act (No 20,285), the Undersecretary of Public Health was asked if it maintains a central stock of injectable isoniazid or rifampicin and responded that they do not manage a reserve of these medications, which are requested by each Health Service in the country to the National Supply Center (CENABAST), located in the Metropolitan Area. In a subsequent request to CENABAST on the delivery of injectable isoniazid or rifampicin to different Health Services in the years 2023 and 2024, data was received on 33 shipments for that period, detecting a median delivery time of 4 days with an IQR of 2 -8 days (range 0-12 days). In addition, one must consider the additional time it takes to submit the application to the central level to obtain authorization for the use of these injectable drugs. The survey to CENABAST also indicated that as of December of each year between 2020-2024 there was no stock available for these injectable drugs. These data reveal that access to conventional injectable anti-tuberculosis drugs in Chile is reactive and has a delay that could be clinically relevant.

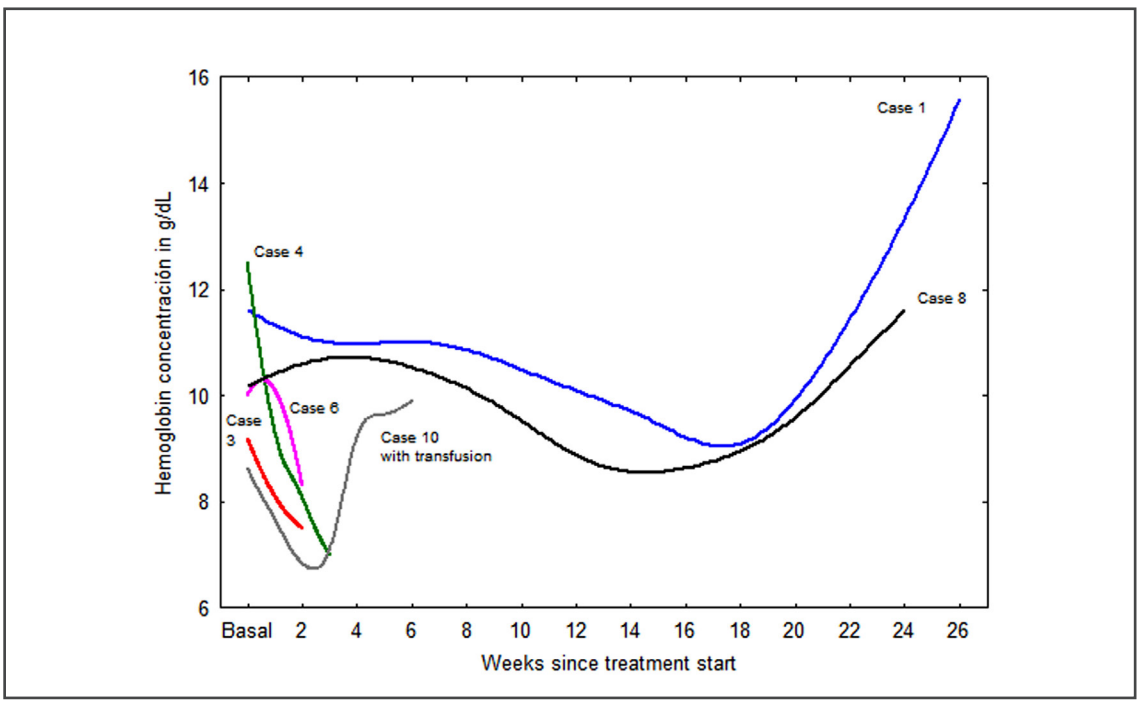

Figure 1: *Trends in hemoglobin concentration in 6 patients treated for ≥1 week with linezolid. Curves were fitted by locally weighted scatterplot smoothing (Lowess) using the software package Statistica 8.0 StatSoft, Inc.*

Table 3. Place of hospitalization, outcome and final WHO treatment classification for 10 patients treated with meropenem, linezolid and quinolones for non-drug resistant tuberculosis. Hospital Valdivia, Chile, 2020-2024.

Case	Place of hospitalization and outcome	WHO TB treatment outcome, details
1	General ward. Favorable evolution Complete treatment on an outpatient basis, Anemia secondary to linezolid	Treatment success
2	ICU, Mechanical ventilatory support. Switched to standard therapy by nasogastric tube after initial stabilization but died 2 weeks admission after	Died Cause of death: Multiorgan failure
3	General ward. Switched to standard therapy after laboratory normalization. Anemia secondary to linezolid	Treatment success
4	Intermediate Care Unit. Switched to standard therapy after laboratory normalization, Anemia secondary to linezolid. He developed upper gastrointestinal bleeding after discharge and refused readmission	Died during continuation phase. Cause of death: Anemia due to upper gastrointestinal bleeding
5	Intermediate Care Unit Died in hospital 24 hours after admission. Cause of death: Shock and liver failure	Died
6	General ward. Switched to rifampicin, ethambutol and levofloxacin after hepatic improvement. Mild thrombocytopenia secondary to linezolid	Treatment success
7	General ward. Switched to standard therapy	Treatment success
8	General ward. Achieves temporary microbiological control and is transferred to rifampicin + ethambutol in the continuation phase with subsequent discharge. Anemia secondary to linezolid	Lost of follow-up with therapy abandonment
9	ICU. Management with non-invasive mechanical ventilation. Died 4 days after admission	Died Cause of death: Respiratory failure
10	Intermediate Care Unit. Favorable evolution Switched to isoniazid, pyrazinamide and ethambutol	Under treatment

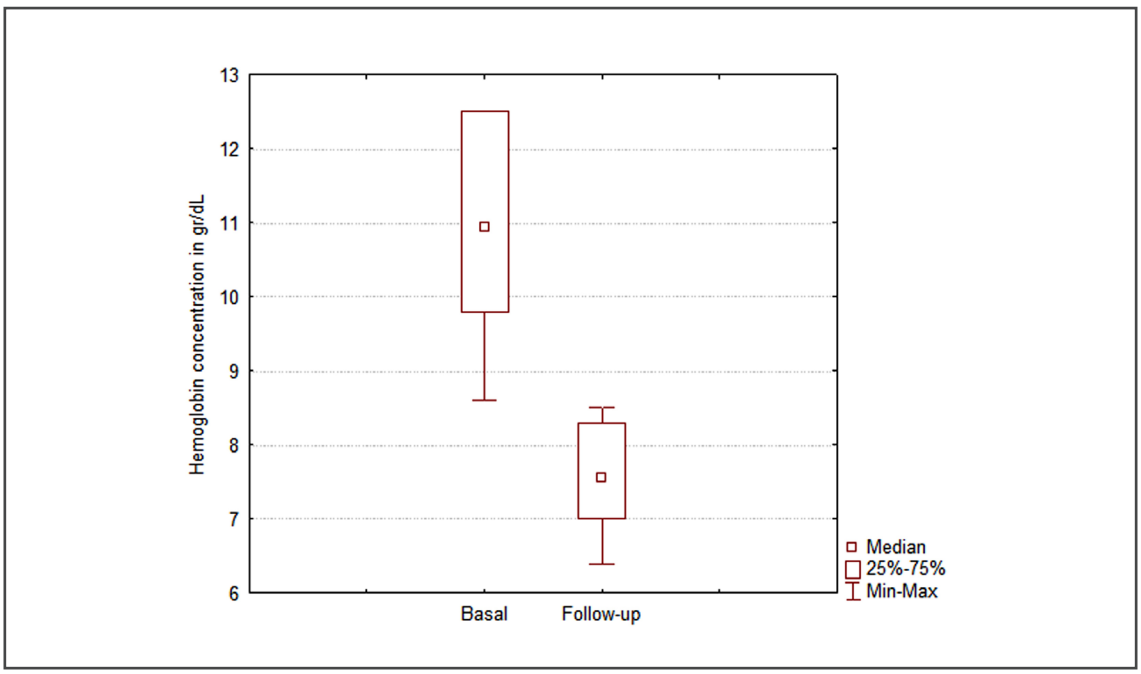

Figure 2: *Changes in hemoglobin concentration in 6 patients with prolonged use of linezolid for TB treatment, Hospital Valdivia, Chile, 2020-2024. Median, lower (25%) and upper (75%) interquartiles values are indicated.*

Discussion

The results of this series indicate that the combined use of meropenem, linezolid, and quinolones is a viable option for managing hospitalized patients with tuberculosis who have various contraindications to the use of standard oral treatment and may contribute to microbiological control and patient cure. However, in some cases, its application was a desperate measure, and in others, it was associated with hematological adverse reactions. The main reasons for using this alternative were severe adverse reactions associated with rifampin or isoniazid, severe hepatitis or liver failure, critically ill patients, or the unavailability of the oral route, which may involve non-invasive mechanical ventilation, fasting due to suspected gastrointestinal bleeding, and gastrointestinal symptoms. These conditions are common in hospitalized patients with tuberculosis.

All strains of *M. tuberculosis* possess an Ambler class A beta-lactamase called BlaC, which is constitutively synthesized and confers resistance to most beta-lactams. However, meropenem is a poor substrate for this enzyme, with some capacity to inhibit it and is also active against non-replicating *M. tuberculosis* microorganisms. The addition of clavulanic acid significantly reduces the MIC for meropenem and achieves a bactericidal effect after two weeks, making it an alternative for cases of drug-resistant *M. tuberculosis* infections[1,10,11,12]. The addition of clavulanic acid to imipenem does not result in as stable and universal reductions in MIC as with meropenem[10]. In contrast, ertapenem has no synergistic activity with clavulanic acid and does not achieve an early bactericidal effect in patients treated with this compound[11]. The combination with clavulanic acid (typically as 3 daily doses of amoxicillin-clavulanate 500/125 mg) is associated with gastrointestinal intolerance and treatment abandonment in non-critical patients, making it difficult to apply in scenarios like those

described in our patients. The recommended daily dose of meropenem is 6 g, which has greater early bactericidal activity compared to lower doses but was only administered in 3 of our patients. The brief use of these regimens, their combination with other useful compounds, and cultures becoming negative using only 3 grams daily in one case with prolonged therapy[5], do not suggest that a lower dose significantly influenced a worse outcome. Furthermore, the recent availability of plasma meropenem level measurement locally will allow us to more accurately determine the required dose for each case in the future. There are no nationally reported MIC values of *M. tuberculosis* for meropenem, and described series indicate a wide range, with MIC50 ≥16 µg/mL when not combined with clavulanic acid[13]. The addition of clavulanate reduces the meropenem MIC90 to 8 µg/mL[14]. This evidence suggests to add the beta-lactamase inhibitor in alternative therapy whenever possible, after assessing the patient's gastric tolerance and absorption. In this sense, the trough meropenem level detected in our patient that was not associated with clavulanate, was probably subtherapeutic.

The recommended dose of linezolid is 600 to 1200 mg/day, but the higher dose is associated with myelo- or neurotoxic effects (peripheral or optic polyneuropathy) in cases of prolonged use, as observed in our patients[1]. Specifically, myelotoxicity is linked to a trough concentration >8 µg/mL, and these levels are more likely to occur with 1.200 mg/day of linezolid than with 600 mg/day (23% vs. 2%, respectively)[15,16]. However, limiting the dose to 600 mg/day is not so simple, as only 1.200 mg/day provides an adequate PK/PD ratio (AUC/MIC of 119 for linezolid as a free drug), which is associated with microbiological efficacy and minimizing the risk of resistance emergence[17]. This is due to the drug's pharmacokinetic variations along with the wide range of MICs for linezolid in *M. tuberculosis* strains. For strains with MIC <0.5 µg/mL, this AUC/MIC target is achieved in >95% of cases with 1.200 mg/day but only in 72% of cases with a MIC of 1 µg/mL[17]. In critically ill patients, linezolid concentrations are even more variable due to increased renal clearance, body size, certain types of renal replacement therapies, and the inhibitory or inductive effect of some drugs on P-glycoprotein (P-GP). This P-GP acts as an efflux pump that affects drug bioavailability[18,19,20]. For example, rifampicin induces the expression of P-GP, reducing absorption and increasing elimination of linezolid, a drug interaction detected in one of our patients even several days after rifampicin was discontinued[19,20]. Other drugs that decrease linezolid concentrations include phenobarbital, levothyroxine, and venlafaxine[19]. In contrast, drugs such as clarithromycin, digoxin, cyclosporine, proton pump inhibitors, amlodipine, or amiodarone increase linezolid concentrations by inhibiting P-GP expression[19].

Linezolid has adequate penetration into the CNS in adult patients, achieving concentrations similar to plasma levels and a relative AUC of 83% compared to AUC in blood[21]. The narrow therapeutic range of linezolid, variability in its plasma concentrations, drug interactions, and the need to achieve certain PK/PD standards make it essential to monitor its plasma levels whenever possible. However, in Chile, there are no published MIC values for linezolid in *M. tuberculosis* strains, so the AUC/MIC calculation can only be approximate. In cases of drug-resistant TB, using 600 mg/day of linezolid with other drugs maintains the effectiveness of higher doses but with fewer hematological side effects[22].

Moxifloxacin and levofloxacin are useful alternatives and are considered in national guidelines in cases of intolerance/contraindication to first-line drugs or resistant strains[23,24,25]. Both have a bactericidal effect, and in the case of moxifloxacin, it can reduce the viable strain count in sputum by half within 2 days (for comparison, rifampicin reduces the count to a quarter in 2 days)[24]. Levofloxacin, moxifloxacin, and linezolid are bactericidal and sterilizing drugs against *M. tuberculosis* and are key drugs in the alternative treatment of this infection, whether or not associated with resistance to first-line drugs. Meropenem is also bactericidal but has more limited application due to its exclusively parenteral dosing regimen[26,27].

In this study, the administration of intravenous amikacin was not considered, despite the

fact that its MICs for *M. tuberculosis* are ≤2 µg/mL[28,29], which are not very different from those of susceptible *Enterobacteriaceae*. However, pulmonary concentrations of amikacin are insufficient to achieve a bactericidal effect[30], and most of our patients had pulmonary involvement. Therefore, it does not appear to be a relevant alternative until further studies become available.

We believe that communicating this experience is necessary in the current context where hospitalizations of patients with TB are frequent, including cases in critical condition or those with limitations for receiving a standard oral treatment. In our region, one-third of the cases diagnosed between 2011 and 2019 required hospitalization for various reasons, with a high case-fatality rate (close to 20%)[9], highlighting the challenges of providing appropriate therapy without delays in this scenario. The alternative treatment reported in this study, in the absence of resistance to antituberculosis drugs, is likely not an isolated phenomenon, and there is an urgent need to create a national treatment guideline for this context. The current Chilean guidelines are the result of a long historical trajectory and are primarily designed for an outpatient setting[23]. However, they are not well-suited for critically ill patients or situations similar to those experienced by our patients. Additionally, they do not provide alternatives in cases of contraindications to rifampin use, requiring consultation and awaiting advice from the central office of the national TB Program[23]. Furthermore, the mere inclusion of intravenous rifampicin or isoniazid, which is logistically limiting in Chile, does not resolve this problem due to the numerous significant interactions they have with common medications used in critically ill patients such as propofol, midazolam, fentanyl, or amiodarone. These treatments are also not applicable in certain organ dysfunctions or in the presence of certain adverse reactions, as evidenced by our work. Table 4 summarizes some considerations for this therapeutic strategy.

Table 4. Considerations for the use of meropenem-clavulanic acid, linezolid, and quinolones in the treatment of drug-susceptible tuberculosis in special conditions.

Topic	Comments
Setting of use	Only in hospitalized patients for whom it is deemed essential to initiate or continue tuberculosis treatment and when a standard scheme is not feasible: Adverse drug reaction, mainly to rifampicin or isoniazid; severe hepatitis o liver failure, critical ill patients, unavailability to use oral route. It is recommended to apply a triple therapy with meropenem ± clavulanic acid, linezolid, and quinolones Resume standard treatment as soon as possible Consult the Central Office of the Tuberculosis Control and Elimination Program for other therapeutic alternatives
Administration route	Quinolones and linezolid can be used orally or by intravenous route. However, the oral route is not recommended in cases of digestive surgery, nausea or vomiting, diarrhea, or impaired consciousness. In the case of respiratory failure with non-invasive mechanical ventilation with high-flow nasal cannula or continuous positive airway pressure, there are limitations to receiving oral treatment.

...continued table 4.

Topic	Comments
Meropenem	Consider using 6 g/day in 3 doses. Adjust in case of renal failure. Monitor the hematological series periodically due to the risk of neutropenia. Do not use meropenem as the sole anti-tuberculosis drug. Evaluate feasibility of adding oral amoxicillin-clavulanate (500/125 mg TID)
Linezolid	Dose range: 600-1200 mg/day. Prefer starting with the lower dose. Use the lower dose in the presence of severe anemia, thrombocytopenia, renal failure, renal replacement therapies, and concomitant use of proton pump inhibitors, digoxin, amiodarone, or cyclosporine. If available, request pre-dose plasma level measurement and estimate the 24h-area under the curve (AUC24). Desirable pre-dose concentration range: 2-8 ug/mL. Higher values increase toxicity. Suggested AUC/MIC ratio: 119. Assume MIC of 0.5 ug/mL. Avoid combined use of linezolid with rifampicin. Separate use by at least one week. Monitor the hematological series periodically for the risk of anemia and thrombocytopenia. Do not use linezolid as the sole anti-tuberculosis drug. Avoid co-administration with serotoninergic psychiatric drugs, due to increased risk of serotonin syndrome.
Quinolones	Levofloxacin (750 mg/day) or moxifloxacin (400 mg/day). Adjust the dose of levofloxacin in case of renal failure. Evaluate the risk of chelation, cytochrome interaction, or QTc prolongation with the use of other concomitant medications. Do not use quinolones as the sole anti-tuberculosis drug.

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