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THE VALUE OF THERAPEUTIC DRUG MONITORING OF LINEZOLID IN CLINICAL PRACTICE

Linezolid, a synthetic oxazolidinone antibiotic, is frequently used for the treatment of serious gram-positive infections including *Staphylococcus aureus* and enterococci. It is also commonly used as part of long-term treatment regimens for mycobacterial infections, nocardiosis and prosthetic joint and bone infections. While its high oral bioavailability and targeted spectrum make it valuable, its **narrow therapeutic index, variable pharmacokinetics,** and **potential for exposure-dependent toxicity** underline the importance of **therapeutic drug monitoring (TDM).** TDM can assist in personalizing dosing to maximize efficacy (clinical outcomes) while minimizing linezolid-induced adverse effects.

Why Consider TDM for Linezolid?

1. **Preventing Toxicity: prolonged (>7 days) or high concentrations increase the risk of toxicity**
   - **Haematologic Toxicity:** linezolid is associated with **thrombocytopaenia, anaemia, and pancytopaenia,** especially in critically ill patients or those with renal impairment.
   - **Neurologic Toxicity:** Prolonged exposure can lead to **optic neuropathy and peripheral neuropathy.**
   - **Mitochondrial Toxicity:** Mitochondrial protein synthesis inhibition is dose- and duration-dependent, monitoring for **lactic acidosis** development is important in patients on linezolid.
2. **Ensuring Efficacy**
   - **Subtherapeutic levels** can result in treatment failure, especially in **deep-seated infections,** obese patients, or patients with augmented renal clearance (ARC).
   - TDM enables individualized dosing to maintain optimal **AUC_{24h}:MIC ≥ 80–120** targets, associated with clinical success. There is a linear relationship between AUC_{24h}:MIC and C_{min}, hence trough concentrations can be used as a proxy for the desired pharmacokinetic-pharmacodynamic (Pk-Pd) target.
   - Reduces risk of antibiotic resistance development.
3. **Addressing Pharmacokinetic Variability**
   - Pk variability is influenced by multiple variables including **age, weight, renal function, inflammation, co-medications,** and critical illness.
   - In **ICU patients**, linezolid clearance can be unpredictable, warranting closer monitoring.

How Is Linezolid TDM Performed?

- **Target Trough Concentration (C_{min}):**
  - Recommended range: **2–7 µg/ml**
  - Troughs >7 µg/ml associated with haematological toxicity
  - Troughs <2 µg/ml increases risk of treatment failure
- **Sampling Time:**
  - Trough sampling is typically done after **steady state** is reached **(after 5 doses)**
  - Trough sample: ideally just before next dose (within 30 minutes)
  - Record the dosage, date and time of last dose (required for interpretation of level)
  - Following a dosing modification it is **important to wait for new steady state** (after 5 doses of modified dose) before repeating the level.
- **Frequency:**
  - Baseline (after 5 doses)
  - Weekly during prolonged therapy
- **Analytical Method:**
  - Quantification via **LC-MS (the gold standard, performed at PathCare)**

How to interpret?

There are potentially many variables influencing the measured concentration and it is important to consult across disciplines to meaningfully interpret results.

- Ensure compliance including correct dose and timing of dose
- Look for potential drug interactions that could impact on linezolid absorption or clearance e.g. rifampicin induces linezolid clearance
- For sub-therapeutic or toxic levels it is recommended to seek expert guidance and consult with a clinical microbiologist, clinical pharmacist and/or clinical pharmacologist

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Who Should Be Monitored?

TDM is particularly valuable in:

- **Critically ill** or **ICU** patients
- **Renal impairment** or **dialysis**
- **Baseline cytopenias (myelosuppression, thrombocytopaenia, anaemia)**
- **Obese** or **underweight** patients
- **Anticipated/ prolonged therapy** (>7 days)
- **Concomitant serotonergic agents** (risk of serotonin syndrome)
- **Concomitant rifampicin use** (~30–65% drop in Linezolid exposure)
- Patients with **treatment failure** or suspected **toxicity**

Evidence Supporting Linezolid TDM

- **Lau et al., 2023**: Demonstrated that appropriate dose adjustment significantly reduced the odds of linezolid toxicity in patients on prolonged treatment.
- **Crass et al., 2019**: Highlighted association between renal impairment and toxicity, with dose adjustments using TDM improving the probability of achieving optimal exposures.
- **Pea et al., 2010**: Showed a 33% reduction in linezolid-induced thrombocytopaenia with TDM-guided dose adjustment in adult patients.
- **Zoller et al., 2014**: Highlighted underexposure in ICU patients with ARC, advocating for personalized dosing.
- **Hashimoto et al., 2018; Yan et al., 2023**: Concomitant rifampicin co-treatment lowered linezolid exposure by ~30–65% (AUC & trough), supporting TDM in all such patients.
- **Local data (PathCare, 2025):** Total of 56 samples for linezolid TDM: 62.5% in toxic range requiring dose adjustment; only 20% of samples within the 2-7μg/ml optimal range.

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INTEGRATING TDM INTO PRACTICE

1. Recognize and request

Order TDM in at-risk patients and ensure correct trough sampling at steady state

2. Interpret and adjust

Collaborate with the antimicrobial stewardship team to interpret results and adjust dosing

3. Document and monitor

Record results and dose changes, and monitor for clinical response

KEY TAKEAWAYS

Linezolid TDM enhances both safety and efficacy

Consider especially in long-term therapy and critical illness

Aim for trough levels between 2–7 μg/ml

Collaborate across disciplines to optimize outcomes