MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

LINEZOLID THERAPEUTIC DRUG MONITORING RECOMMENDATIONS

Recommendations:

- Serum trough goal:
  - 2 to 8 mg/L
- Linezolid Therapeutic Drug Monitoring (TDM) is recommended in the following scenarios:
  - Anticipated duration of therapy > 2 weeks. TDM may be considered in case-by-case scenarios with shorter durations in patients with significant risk factors for supratherapeutic levels and/or pre-existing thrombocytopenia. TDM may reasonably not be performed in patients without significant risk factors for thrombocytopenia and/or durations at borderline risk.
  - In the presence of significant enzyme inducers, especially rifampin
  - After any TDM-guided dosing change
- Timing:
  - Trough, after 4-5 doses of the current regimen. For inpatients with a plan for linezolid on discharge, TDM prior to discharge is preferred.
- Dose adjustments:
  - May be made assuming linear pharmacokinetics, but formulation considerations also need to be taken into account. The 600mg tablets may be cut in half with a pill cutter if needed. Liquid is also available but may be more expensive. ID pharmacy should always be involved in such decisions.
- How to Order:
  - Search for Linezolid in MiChart test listing (ADLIN is the lab test code). Typical turn-around time is 2 business days.
- Stewardship Pharmacy:
  - When ordered, email sendouts and phlebotomy to let them know, to optimize likelihood of both the level being drawn as well as being sent appropriately. Process would be letting group know, phlebotomy would respond that the order is acknowledged and assign to a phlebotomist, then sendouts would reply that the test was in fact received. The email address for the group is path-misc-sendouts@med.umich.edu. Members should include the following:
    - Owners:
      - Mary Tocco – Manager Onsite Phlebotomy
      - Beth Lawless – Senior Medical Technologist Specimen Processing
      - Brian Tapp II – Quality Assurance Coordinator Onsite Phlebotomy
    - Members:
      - Carla Bigham – Supervisor UH IP Phlebotomy
      - Ann Rosin – Supervisor CW IP Phlebotomy
      - Michelle Merkel – Supervisor Specimen Processing
      - Kimberly Fera – Associate Supervisor UH IP Phlebotomy
      - Kelly Pruitt – Associate Supervisor UH IP Phlebotomy
      - Shirley Whittaker – Associate Supervisor UH IP Phlebotomy
      - Heidi Lewis – Associate Supervisor CW IP Phlebotomy

Rationale:

- *Trough correlation with thrombocytopenia*: Duration of therapy is a well-characterized risk for development of thrombocytopenia, with durations > 2 weeks typically being espoused as being at increased risk. However, several studies have also identified trough concentrations as being a significant, independent predictor of thrombocytopenia development. In a cohort of Chinese patients, a Cmin < 6 was identified as a target, with 50% of patients with troughs exceeding this value developing thrombocytopenia (Dong HY et al., Eur J Clin Microbiol Infect Dis 2014). In Japanese patients, a threshold of 8.2 mg/L was identified (Matsumoto K et al., Int J Antimicrob Agents 2014). In a study of 50 Italian patients, significantly higher trough values were noted in patients who developed thrombocytopenia compared with those who did not, with a mean

value of ~9 mg/L in those who did develop abnormalities (Cattaneo D et al., Int J Antimicrob Agents 2013). *This has led to a proposal for an upper trough bound of 8-10 mg/L.* These, and other studies also identify substantial variability in linezolid trough levels. For example, in Italian cardiothoracic surgery patients, 45% of patients had levels outside a therapeutic range of 2-8 mg/L, with most (~80%) patients having supratherapeutic levels (Pai MP et al., Clin Infect Dis 2023).

- *Trough correlation with efficacy*: Both in vitro and clinical data suggest that the concentrations associated with thrombocytopenia are in excess of those necessary for optimal efficacy. A neutropenic thigh infection model identified %T > MIC 80-100% as predictive of efficacy against experimental infection due to *S aureus* (Andes D et al., Antimicrob Agents Chemother 2002). No equivalent data is available for vancomycin-resistant *E faecium*. However, in a pharmacodynamic analysis of 288 adult patients who received linezolid under a compassionate use program, this %T > MIC threshold was found to associated with both microbiological and clinical cure in a range of infections, most of which were due to VRE (Rayner CR et al., Clin Pharmacokin 2003). Given that the MIC90 of *S aureus* to linezolid is 2 mg/L, and the CLSI breakpoint for *Enterococcus* is also 2 mg/L, this has led to a proposal for a trough lower bound target of 2 mg/L, which would thus achieve 100% T > MIC. Note, however, that the CLSI breakpoint for linezolid and *S aureus* is 4 mg/L. As such, while 2 mg/L should generally be an appropriate efficacy target, the target should likely be 4 mg/L in the rare scenarios when the *S aureus* MIC is 4 mg/L.

- *Additional information*:
  - Risk factors associated with supratherapeutic levels include concomitant cyclosporine (Pai MP et al., Clin Infect Dis 2023), omeprazole, amiodarone, or amlodipine (Pea F et al., Antimicrob Agents Chemother 2010), and renal insufficiency, especially eGFR < 60 mL/min (Crass RL et al., Antimicrob Agents Chemother 2019). Elderly patients (> 70 years old) or those with BMI < 20 may also be at risk. Conversely, repeated studies have shown that rifampin substantially reduces linezolid exposures, and thus co-administration is not recommended (Bock M et al., J Antimicrob Chemother 2023). It is assumed, but not known, that other significant enzyme inducers (phenytoin, carbamazepine, phenobarbital, efavirenz, for example) may exert a similar effect.
  - Limitations of the data at this time are a lack of data in patients in the United States and also limited data prospectively validating TDM. In one study of 35 patients in Italy, 18 patients developed thrombocytopenia after a median duration of linezolid of 21.5 days. In 6 of these patients, dosage reductions allowed for completion of therapy. The timing of identification of supratherapeutic levels relative to development of toxicity is not clear from this study (Pea F et al., J Antimicrob Chemother 2012). In a study from Australia, appropriate dose adjustment with first TDM (performed a median 5 days after initiation of therapy) was associated with decreased toxicity, but details about what toxicity and how many patients continued to experience toxicity despite adjustment are not available (Lau C et al Int J Antimicrob Agents 2023).

- *Conclusion*: %T > MIC 100% is a reasonable PD threshold for linezolid. For most patients, this would correspond to a trough target of 2 mg/L. Trough levels significantly higher than that, especially those > 8-10 mg/L, are associated with thrombocytopenia, and depending on the patient population, may occur in a substantial proportion of patients. As a result, linezolid TDM is reasonable for patients at risk of thrombocytopenia. The lack of prospective validation is a significant limitation at this time.

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